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AN OUTLINE OF RECENT ADVANCES IN THE EXPERIMENTAL PRODUCTION OF TUMOURS.[1]

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DURING recent years a large number of pure chemical substances with cancer-producing properties have been prepared either synthetically or by extraction from coal tar, oils and other naturally occurring mixtures, and many kinds of malignant tumours, closely resembling their human counterparts, have been produced experimentally in animals by means of these substances or by other carcinogenic agents. Such diverse tumours as carcinomata of the skin, liver, bladder, breast and lung, sarcomata of bone and soft tissues, and gliomata of the brain have been produced experimentally. The remarkable results achieved in this field show how uninformed are those who criticize experimental cancer research as unproductive.

Much of the recent research work on the experimental production of tumours has been published in special journals which few general practitioners read. The present paper is an attempt to epitomize some of the most important sections of this work, and to indicate the probable trends of future research. For greater detail the excellent papers of Cook and co-authors (1936), Kennaway and Kennaway (1937), Cook and Kennaway (1938 and 1940), and the valuable monograph by Hueper (1942), should be consulted.

THE CARCINOGENIC HYDROCARBONS.

Occupational Skin Cancers.

It is over 150 years ago since Percival Pott described the first clearly recognized occupational skin cancer, chimney sweep's cancer of the scrotum, a tumour which recent researches have shown to be due to carcinogenic substances present in soot. Later, in the second half of last century, the prevalence of occupational skin cancer in those who handled tar, oils and crude paraffin was recognized. One of the most striking instances was among mule-spinners, in whom carcinomata of the skin of the scrotum, thighs or lower parts of the abdomen frequently developed, clearly as a result of constant contact of these parts with lubricating oil (Brockbank, 1941).

Experimental Tar and Oil Cancer.

Recognition of these occupational tumours naturally led to attempts to produce tumours experimentally in animals by similar agents. As long ago as 1889 Hanau painted rats with tar, but failed to evoke tumours. We now know that rats are very resistant to carcinogenic substances applied to the skin, and had Hanau used mice instead of rats, he would have forestalled the first successful experiment by a quarter of a century.

It was the good fortune of two Japanese workers, Yamagiwa and Ichikawa, to apply a suitable agent to a susceptible animal for a sufficiently long time. In 1914 they reported the production of papillomata and carcinomata in rabbits' ears following the long-continued application of tar. It was only after the Great War of 1914-1918, however, that general interest in the subject was aroused. Thereafter, experimental tar cancer was studied exhaustively (Woglom, 1926). In 1922 Leitch first demonstrated experimentally the carcinogenic properties of shale oil and lubricating oil.

The Search for the Carcinogens in Tars and Oils.

The Potency of Tar Fractions.

Since tars vary in carcinogenic activity, and since they are complex mixtures of substances, attempts were made to concentrate the potent agent. In 1923 Kennaway fractionally distilled carcinogenic tars, and showed that the carcinogenic factor was in the higher-boiling fractions.

[1] Read at a meeting of the Alfred Hospital Clinical Society on December 7, 1944.

Artificially Produced Carcinogenic Mixtures.

Kennaway next showed that potent carcinogenic tars could be made artificially by heating a great variety of organic substances—skin, muscle, yeast, cholesterol, acetylene—to temperatures over 700° C.; and that a non-carcinogenic petroleum could be made carcinogenic by heating it to 800° C. (Kennaway, 1930).

Fluorescence Spectra.

In 1930 Hieger, working with Kennaway, made the important observation that the fluorescence spectra of carcinogenic tars and oils had characteristic bands, which were closely like those of the spectrum of the hydrocarbon 1:2-benzanthracene. The latter, however, was found to be not carcinogenic. Accordingly, Kennaway made a special study of a series of pure hydrocarbons allied to 1:2-benzanthracene, and found 1:2:5:6-dibenzanthracene to be active in producing tumours when applied to the skin of mice. At last a chemically pure carcinogenic substance had been identified, not indeed as a constituent of tar, but as a result of painstaking studies of the physical characters of carcinogenic tars.

Pure Carcinogenic Hydrocarbons.

The importance of the discovery of pure carcinogenic hydrocarbons (see Figure I) by Kennaway and Hieger can scarcely be exaggerated. It gave a tremendous impetus to research; many new carcinogenic compounds were soon produced; and tar-cancer research was largely superseded by more precise researches with these pure substances. Foremost in this work have been Kennaway and his staff in London, and the school of American workers at Harvard.

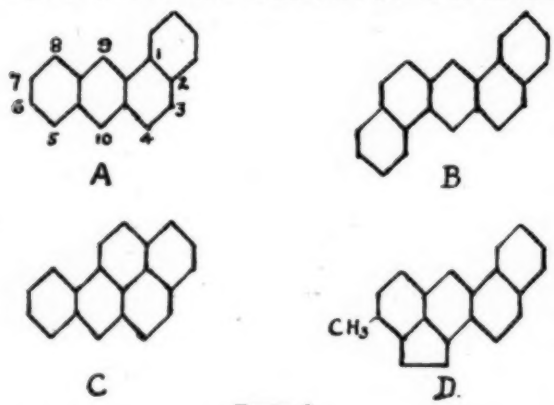

Figure I.
A = 1:2-benzanthracene; B = 1:2:5:6-dibenzanthracene; C = benzpyrene; D = methyl-cholanthrene.

Dibenzanthracene.

Dibenzanthracene is now chiefly of interest as being the first discovered pure carcinogen. It is much less potent than the following substances.

Benzpyrene.

Benzpyrene is the most active, perhaps the only important, carcinogenic substance in coal tar. It has been prepared both by isolation from tar and synthetically. It is a highly potent carcinogen, producing skin tumours in a high percentage of mice after a relatively brief induction period.

Methyl-Cholanthrene and Cholanthrene.

Methyl-cholanthrene and cholanthrene merit special interest, not only because they are highly potent carcinogens, but also because they are closely related chemically to the bile acids, from which they can easily be prepared. From their structural formulæ it will be seen that these compounds are really 1:2-benzanthracene derivatives with substituents in the carcinogenically favourable positions 5, 6 and 10.

Other Carcinogenic Hydrocarbons.

Recent researches have shown that many of the simple substitution derivatives of 1:2-benzanthracene are potent carcinogens. This applies particularly to those with substitution groups at the 5, 6, 9 and 10 positions of the benzanthracene nucleus. The most potent of all are those compounds with substituents at two of these positions; thus 9:10-dimethyl-1:2-benzanthracene is the most active carcinogenic substance so far discovered, with a potency nearly twice that of the cholanthrenes and about six times that of dibenzanthracene.

Sarcomata Produced by Hydrocarbons.

Before the discovery of the pure carcinogenic hydrocarbons, it had been shown that subcutaneous injections of tar could produce sarcomata. By the use of the pure substances, however, the experimental production of sarcomata of various tissues has been much more closely and accurately studied. The first successful experiment of this kind was that of Burrows, Hieger and Kennaway in 1932; later researches of note include those of Haagensen and Krehbiel (1936), of Shear (1936 and 1938), of Orr (1939), and of Bonser and Orr (1939).

Of special interest are some results obtained by Shear. He produced subcutaneous sarcomata in mice by the introduction of cholesterol pellets containing measured amounts of dibenzanthracene, and he found that 0·0004 milligramme of this substance could evoke a transplantable sarcoma. This is the smallest effective dose of carcinogen so far recorded, and it shows how difficult it might be to isolate and identify naturally occurring carcinogenic substances in tissues.

The production of sarcomata by the same agents which evoke tumours in epithelial tissues is of great interest with regard to the nature of neoplasia. It suggests that, in spite of the great diversity in the origin and behaviour of tumours, the neoplastic change is probably fundamentally similar in all tissues, and that gains in our knowledge of the nature of this change in any one tissue will probably shed light on the entire cancer problem.

Visceral Tumours Produced by Hydrocarbons.

By Local Application.

By the direct introduction of carcinogenic hydrocarbons, by repeated injections, or by the implantation of cholesterol pellets containing the carcinogen, a great variety of visceral tumours has been produced. These include carcinomata of the kidney, liver, epididymis, uterus, prostate and breast, and various types of glioma of the brain.

By Remote Application.

It is of great interest that a carcinogenic substance applied to one part of the body may be absorbed and may then participate in evoking a tumour of some susceptible tissue remote from the site of application. Thus in 1925 Murphy and Sturm first observed that in a high proportion of mice receiving tar applications to the skin epithelial tumours of the lungs developed; this result has been repeatedly confirmed by the use of pure carcinogenic hydrocarbons introduced by various routes, including the intravenous route (Shimkin, 1939). Similarly, Burrows has adduced evidence that the incidence of uterine carcinoma in the rabbit (the commonest spontaneous carcinoma in this animal) can be increased by either local applications or remote subcutaneous or intravenous injections of a carcinogen. So also, Mider and Morton (1939) and others have observed that, in strains of mice subject to spontaneous lymphoid tumours, skin painting with methyl-cholanthrene hastens the development of these tumours.

Pure Carcinogens other than Hydrocarbons.

Barry and other co-workers with Kennaway, in summarizing their researches up to 1935, were careful to point out that their work had been mainly with polycyclic hydrocarbons and closely related substances, and that "there may be other classes of carcinogenic substances of quite different chemical type from those with which we

have been concerned". Several groups of such substances, carcinogenically active for certain tissues, have been identified during the past decade.

Azo-Compounds and Liver and Bladder Tumours.

The first azo-dye to be used in experimental cancer research was scarlet-red, which Fischer in 1906 found to be capable of evoking tumour-like proliferation of the epidermis. Such proliferation, however, was not truly neoplastic, for the changes regressed when the injected dye was absorbed and progressive growth was never obtained. Indeed, the dye soon came into clinical use as an application to stimulate the epithelialization of healing ulcers; and the parent compound o-aminoazotoluene also was put to similar use.

In 1924, Schmidt made the first observation of hepatic tumours attributable to an azo-compound. After feeding scarlet-red to mice, he saw hepatic adenomata, which he suggested had been evoked by the dye during its excretion by the liver. Confirmation and extension of Schmidt's work did not come until 1931 and later, when Yoshida and other Japanese workers showed that o-aminoazotoluene, when given orally or by injection to rats or mice, was highly active in producing adenomata and carcinomata of the liver. (Review by Shear, 1937.) In animals receiving this dye papillomata or carcinomata of the bladder also developed; and vesical and hepatic tumours might occur in the same animal. Tumours were never produced in the tissues at the site of injection of the dye, the carcinogenic activity of which thus appears to be specific for the epithelia of the liver and urinary tract.

In 1937 Kinosita found that liver tumours could be speedily induced also by the ingestion of dimethyl-amino-azobenzene, a dye known as "butter-yellow". This was confirmed by others, including Orr (1940), whose paper is a valuable source of reference.

Beta-Naphthylamine and Bladder Tumours.

The occupational incidence of papilloma and carcinoma of the bladder in workers in the aniline dye industry was recognized many years before its experimental confirmation by Hueper and co-workers in 1938. These workers showed that vesical tumours could be induced in dogs by prolonged feeding with β-naphthylamine, a compound related to aniline and frequently present in aniline products. The specific carcinogenic activity of this substance for the epithelium of the urinary tract was confirmed by Bonser (1943). Hueper's book contains an excellent review of the whole subject of the occupational tumours of aniline workers, and of their experimental counterparts. While β-naphthylamine is the main substance so far incriminated, it is probable that other aromatic amines or their derivatives will also prove to be carcinogenic; and it must not be forgotten that, as has been mentioned above, a few compounds unrelated to aniline can also evoke urinary tract tumours.

A Sarcoma-Producing Quinoline Compound.

While studying the efficacy of trypanocidal substances in laboratory animals, Browning and co-workers (1936) accidentally discovered that one of the substances studied, a complex quinoline derivative quite unrelated to the carcinogenic hydrocarbons, evoked sarcomata at the site of injection.

A Review of Substances Tested for Carcinogenic Powers.

Enough has been said to indicate that, in view of the constant increase in the number and variety of synthetic organic compounds handled and eaten by civilized human beings, thought must be given to the possible carcinogenic effects of some of these. Already, within the last two decades, as we have seen, several distinct classes of potent carcinogenic compounds have been identified; it is certain that future research will reveal similar potency in other classes of compounds as yet not suspected of it.

Much experimental work has already been done in the search for possible carcinogens among pure chemical substances. The United States National Cancer Institute has recently issued a valuable tabular "survey of compounds which have been tested for carcinogenic activity", compiled by J. L. Hartwell. This survey covers 696 substances which have been tested, 169 of which have been found to be carcinogenic. These, of course, include the carcinogenic hydrocarbons and other compounds described above, many of which were tested in the course of deliberate search for likely carcinogenic agents. The future will witness a great expansion of such biological testing of synthetic substances old and new, and of the by-products of industrial and technological processes.

The Experimental Production of Mammary Tumours.

Early Work on the Relation of Mammary Tumours to Ovarian Function.

Struck by the frequency of mammary tumours in the female breast and their great rarity in the male, and perhaps by the acceleration of growth of mammary cancers during pregnancy and lactation, clinicians long ago suspected some relationship between ovarian activity and breast tumours. Towards the end of last century, oophorectomy was advocated as a therapeutic measure in cases of mammary cancer. Experimental researches on spontaneously occurring breast tumours in animals, and the identification of the ovarian hormones, soon led to more precise knowledge in this field.

In 1916 Lathrop and Loeb found that removal of the ovaries of mice before the age of six months greatly diminished the liability of the animals to the later development of mammary cancer as compared with intact control animals. This was confirmed by Cori in 1927, and by Murray in 1928; Murray showed also that, while intact or castrated male mice never developed breast cancer, 7% of castrated males into which ovaries had been grafted developed breast tumours.

Œstrin and Breast Cancer.

The discovery in 1929 of methods of preparing the ovarian hormone, œstrin, in a pure form, opened the way to more exact study of the problem of the association between ovarian activity and the genesis of cancer of the breast.

In 1932 Lacassagne obtained mammary carcinomata in male mice by giving large weekly subcutaneous injections of œstrone benzoate. This result, which was soon confirmed by Burrows (1935), Bonser (1936), and others, is a major landmark in the history of cancer research, for it was the first discovered instance of the experimental production of a tumour by the agency of an endogenous substance. In mice treated with œstrin, prior to the development of neoplasms the breasts undergo varying degrees of hyperplasia and cystic change closely resembling those of the so-called "chronic cystic mastitis" in the human breast—a disease which every competent pathologist recognizes as a dangerous precancerous condition in many cases.

In a valuable outline of the hormonal ætiology of breast cancer, Cramer (1940) has summarized the experimental evidence which shows that the carcinogenic power of œstrin for mammary tissue is augmented by the adrenocortical hormone, and antagonized by anterior pituitary thyreotropic hormone, by an adrenal medullary hormone, and by the male sex hormone testosterone. He has also outlined researches which have shown that excessive œstrin may evoke tumours in other hormone-controlled organs, such as the uterus, the prostate and the testis. Several workers have described interstitial-cell tumours of the testis following prolonged œstrin administration; pituitary tumours also have been produced in this way.

Duct Stasis and Mammary Cancer.

That purely local factors might operate in the causation of mammary tumours was shown in 1925 by the experiments of Bagg. In a strain of mice of low mammary tumour incidence, he obtained many tumours by rapid breeding accompanied by milk stasis resulting from either non-suckling or ligation of the mammary ducts. More recently (1939) Bagg, working with Hagopian, has con-

firmed and extended his original results, using rats. In these animals also, rapid breeding and the prevention of suckling greatly increased the incidence of carcinomata and fibro-adenomata of the breasts. Duct stasis was prominent in these experiments, as in Bagg's earlier experiments, and the authors suggested that the chemical irritation from retained secretions might have been the immediate cause of the tumours.

Confirmatory experimental evidence of the influence of local duct blockage in the causation of breast tumours has also been obtained by local injury of the nipples of lactating mice. Following such injuries there is a higher incidence of tumours in the affected breasts than in normal organs.

Possible Common Mode of Action of Œstrin and Duct Stasis.

It is, I think, quite likely that the production of mammary tumours by œstrin over-dosage is brought about by local factors similar to those operating in Bagg's experiments. Œstrin over-dosage first produces hyperplastic and cystic changes resembling those of human "cystic mastitis"; and in the experimental lesion, as in the human lesion, duct obstruction and retention of secretions are prominent features. Perhaps, then, the mammary hyperplasia induced by œstrin is finally provoked to neoplasia by a chemical stimulus from these retained secretions, as suggested by Bagg. Further, it is not impossible or even unlikely that this stimulus may be due to identifiable carcinogenic substances generated in the stagnant duct contents. The abundant creamy or pultaceous material often seen in the dilated ducts of the diseased human breast may, under suitable conditions, suffer chemical changes involving the formation of carcinogenic compounds related to those already discussed or belonging to some different class. Biological testing of the stagnant duct contents from cancerous breasts must be undertaken by future research workers.

Heredity and Mammary Cancer.

It has long been recognized that different strains of mice differ greatly in the incidence of spontaneously occurring mammary and other tumours. By close in-breeding from mice of high breast cancer ancestry, it was found possible to obtain breeds in which in 80% or more of parous females mammary tumours developed. On the other hand, by close in-breeding from mice of cancer-free ancestry, a breed in which breast tumours rarely or never developed could be obtained. Before carrying out any work in experimental carcinogenesis, the research worker must know thoroughly the qualities of his particular breed of animals as regards the spontaneous incidence of tumours of the kind with which he is concerned.

Differences in the incidence of spontaneous mammary and other tumours in different strains of animals were at first interpreted as being dependent on purely hereditary or genetic differences. As far as the breast is concerned, however, this view has had to be modified, in the manner now to be described.

The "Milk Factor" and Mammary Cancer.

That the variations in incidence of breast tumours in different in-bred strains of mice do not reflect purely genetic differences is shown by the work of Bittner (1940, 1942). He showed that the incidence of breast cancer in mice was greatly influenced by the source of milk on which they were fed in their infancy. Mice suckled by foster-mothers of a stock with a low incidence of breast tumours later showed a low incidence of breast tumours themselves, even though they might have been the progeny of mothers from a stock of high cancer incidence. Conversely, the progeny of a stock of low cancer incidence, foster-fed by animals from a high cancer incidence stock, later showed a greater incidence of mammary tumours than their ancestry.

According to Bittner's work, then, the "inherited" tendency to cancer of the breast in high cancer incidence breeds is really a combination of two distinct factors—(*a*) a true genetic susceptibility to breast cancer, and (*b*) a "breast-cancer-producing factor" transmitted through the milk of mothers of cancerous stock. The nature of this milk-transmitted influence, whether a hormone, a carcinogenic chemical compound or a virus, remains as yet undetermined.

While these researches on the genetic and milk factors in the causation of breast cancer in mice are of great scientific interest, it is necessary to point out that they may have little direct applicability to the problem of causation of human mammary cancer. The strains of mice in which the genetic and milk factors have been demonstrated are closely in-bred strains; and close in-breeding does not occur in modern civilized human communities. While there have been reported occasional instances of breast cancer occurring in many members of a family, suggesting the existence of a transmitted predisposition to this disease, such instances are exceptional, and there is little doubt that the main causes of human breast disease must be sought in local and hormonal factors operating on the breast tissue of the individual subject.

The Experimental Production of Lung Tumours.

Occupation and Lung Tumours.

That occupational factors play an important part in the causation of carcinoma of the lung is shown by the following facts.

Sex Incidence.

Lung cancer is far more common in men than in women, the ratio varying from about 2·5:1 to 10:1 in different communities. Recently, reviewing my own post-mortem records of proved cases of carcinoma of the lung, I found the subjects to comprise 70 males and 14 females, a ratio of 5:1. This striking sex difference for an organ not concerned with reproduction and not under endocrine control points almost conclusively to the preeminence of occupational or habit factors in causation.

Occupational Differences.

Occupational differences in mortality figures for lung cancer are evident. The highest mortality figures are for masons, metal-grinders and founders. Too much reliance must not be placed on these figures, however, because lung cancer is one of the most difficult diseases to diagnose correctly, and there is certainly a great margin of error in the mortality records.

Special Occupations.

Very striking occupational incidence occurs in certain special occupations. Thus in the cobalt mines of Joachimsthal and Schneeberg, a high proportion of men who have worked in the mines for more than a brief period have been found eventually to develop pulmonary carcinoma. The dust in these mines contains both arsenic and radio-active substances, and these are suspected of being the main causative agents.

There are thus good grounds for searching for occupational factors in the causation of lung cancer and for suspecting inhaled substances as the main offenders. What has experiment to say on this question?

Experiments with Soots and Smokes.

Mice not infrequently develop spontaneous tumours of the lungs, and many experiments have been carried out to determine whether or not inhalation of soots, smokes or exhaust gases of various kinds would increase the incidence of such tumours. So far, most of these experiments have yielded negative or doubtful results; but the technical difficulties in carrying out suitable experiments of sufficient duration are great, and further experiments may yet give more conclusive positive findings. One recent investigation at least strongly suggests that the prolonged inhalation of tobacco smoke may be carcinogenic.

Experiments with Road Dusts.

Of special interest are the researches of Campbell (1934 to 1942) on the carcinogenic activity of inhaled dust from tarred roads. This worker found that prolonged exposure

of mice to such dust greatly increased the incidence of lung tumours; that the tar extracted from the dust with benzene was carcinogenic for mouse skin; but that the tar was not the only component responsible for the increased number of lung tumours, because some increase was still observed when mice were made to inhale the tar-free residual dust after benzene extraction. Campbell therefore proceeded to carry out experiments with the inorganic constituents of road dusts, including silica, oxide of iron and aluminium oxide.

Experiments with Inorganic Dusts.

In his 1940 and 1942 experiments, Campbell found that dusting with silica or with iron oxide trebled the incidence of lung tumours in mice, thus giving experimental support to the statistical evidence of a relatively high incidence of lung cancer in grinders and founders. Experiments with the radio-active dust from the Joachimsthal mines gave a decided increase in lung tumours, though not strikingly greater than with some of the other dusts tested. Campbell pointed out that the view that the great prevalence of lung cancer in these mines was due to radio-active substances has not so far been confirmed experimentally; other factors may be involved.

Conclusions.

Campbell's researches point clearly to the importance of inhaled substances in the genesis of lung tumours. It will be for future research to make more precise our knowledge of the carcinogenic activity of the many and various occupational and other dusts and vapours inhaled by human beings. Enough has already been done to show that both organic and inorganic substances must be investigated, and to indicate the methods to be pursued in this field. In addition, as I have indicated at the end of the first section of this paper, the possible effects of carcinogenic substances absorbed from extra-pulmonary sites and carried to the lungs by the circulation must not be forgotten.

Radiations as Carcinogenic Agents.

The Carcinogenic Action of Light and Ultra-Violet Light.

To Dr. E. H. Molesworth, of Sydney, great credit is due for his clear exposition in 1927 of the clinical evidence showing the carcinogenic power of sunlight. Molesworth's views have now received general endorsement, and over-exposure to ultra-violet rays is now clearly recognized as the most important single factor in the causation of epidermal carcinomata. In accord with this are the following observations: (*a*) the distribution of skin cancers, the common sites being the ears, face, neck and dorsal aspects of the hands and forearms; (*b*) the much greater frequency of epidermal cancers in fair-skinned than in dark-skinned people, especially in those with delicate skins which freckle and sunburn easily; and (*c*) the greater frequency of skin cancer amongst people in sunny countries than amongst similar people in less sunny lands—for example, in Australia as compared with Great Britain, or in the southern as compared with the northern States of the United States of America.

Experimentalists have abundantly confirmed the carcinogenic effects of light and ultra-violet rays on the skin. The first of these was Findlay (1928 and 1930), who produced papillomata and carcinomata of the skin of albino mice by means of ultra-violet rays from a quartz lamp. Confirmatory results in both mice and rats, albino or dark-haired, were soon obtained by many other workers by means of both sunlight and ultra-violet rays. The subject is well reviewed by Hueper. Most of the tumours so produced are situated on the ears, eyes, nose or tail base—that is, on relatively exposed hairless parts. Albino animals are more susceptible than pigmented animals. The induction period varies from three to nine months or longer.

The mode of action of light in producing skin tumours is uncertain. It has been suggested that over-irradiation of sterols in the skin may produce carcinogenic substances; but this is purely speculative, and attempts to produce such substances by irradiating cholesterol have so far failed.

The Carcinogenic Action of X Rays.

Röntgen's discovery of X rays in 1895 was soon followed by the appearance of cases of chronic X-ray dermatitis in exposed persons, and many examples of supervening carcinoma of the skin were reported from 1902 onwards (Hueper, *loco citato*, page 247 *et sequentes*). Even today, although protective measures have been in use for many years, occasional cases of X-ray cancer are to be seen.

Experimental confirmation of the carcinogenic effects of X rays has been made by several workers (see Hueper). The development of sarcomata of the dermis following exposure to X rays has also been observed experimentally as well as clinically.

The Carcinogenic Action of Radio-Active Substances.

One of the most remarkable instances of an occupational tumour yet described was due to radio-active substances. Only a brief outline of the story, told by Martin and Humphries in 1929 and well reviewed by Hueper, can be given here. Girls, who were employed to paint the dials of luminous watches with a paint containing radium and mesothorium, developed the habit of pointing their brushes with the tongue, and so continuously ingested small amounts of the radio-active material. Some of them developed acute radium poisoning, manifested by necrosis of the jaw and aplastic anæmia. Others, who escaped these acute results, died much later from osteogenic sarcomata of various bones. It was eventually proved that these were due to the effect of the radio-active metals, which after absorption, like other heavy metals such as lead, were deposited in and retained by the bones. Some of the skeletons of these girls, exhumed many years later, were still highly radio-active.

Both carcinomata and sarcomata have been caused in human tissues by the local application of radium. A boy, who recently attended this hospital, died at the age of eighteen years from a squamous-cell carcinoma, which commenced about two years ago in the skin of the neck, where there had been the scar of a radium burn at the site of treatment of a small tumour at the age of three years. I know of several similar cases.

Experimental sarcomata of both soft tissues and bones have been produced by many workers by means of radio-active substances. Sabin and co-workers (1932) obtained osteogenic sarcomata in rabbits after intravenous injections of radium and mesothorium, thus demonstrating the experimental counterpart of the sarcomata of watch-dial painters just described. Other workers have produced bone sarcomata by the direct introduction of radium and mesothorium into the femora of rabbits. Subcutaneous sarcomata can be produced in rats and mice by the implantation of radium, and Ross (1936) showed that the γ rays were responsible, for sarcomata were produced when the radium was adequately screened in platinum containers.

In view of the current use of "Thorotrast" (thorium dioxide) in radiological diagnosis, the ready experimental production of sarcomata by this substance is of special interest (see Foulds, 1939). Insufficient time has yet elapsed to know whether or not this may prove to be a risk to human beings also.

Some General Considerations.

The Causation of Human Cancer.

On Causation in General.

In discussing the "causes" of tumours, it is important to clarify our ideas of the meaning of "causation". When we say that "the tubercle bacillus is the cause of tuberculosis", we state only part of the truth, and that the smaller part. The tubercle bacillus does not cause tuberculosis in a test tube, or in some species of animals, or even in some human beings. "Tuberculosis" is the product of the reaction of two reagents, the bacillus and the susceptible tissue into which it is introduced. The intrinsic properties of the tissues which render them susceptible and which are the factors determining their tuberculous reaction are as yet entirely unknown. In this sense, then, the tuberculous reaction to the bacillus is no less "mysterious" than

the neoplastic reaction to a carcinogenic agent. When we can say of a particular tumour: "That tumour resulted from the application of benzpyrene (or ultra-violet rays, or X rays)", then we know every bit as much about its cause as we know about the cause of tuberculosis or of any other inflammatory disease. What makes the neoplastic reaction seem more "mysterious" to us than the inflammatory reaction is its long-delayed and irreversible character, and the fact that it may first manifest itself long after the agent which originally evoked it has ceased to act.

The "Cause" of Cancer.

The "cause" of cancer, a favourite phrase in the public mind and Press, expresses a misconception. There is not one external "cause" of cancer, but a thousand. Cancer is a generic name for a vast group of different diseases. It would be as sensible to seek one "cause" for all inflammatory diseases as to seek one "cause" for all neoplastic diseases. The external cause of a carcinoma of the skin of the face evoked by sunlight is clearly quite different from that of a carcinoma of the liver evoked by an absorbed azo-dye, or of a carcinoma of the stomach evoked by—who knows what dietetic factors Each of the hundreds of kinds of human tumours calls for individual investigation in the search for possible causative factors. And further, several or many quite different causes will be found for tumours of the same kind; thus, we already know that identical carcinomata of the skin may be evoked by the application of a variety of carcinogenic hydrocarbons, by ultra-violet rays, by X rays, and by arsenic. Whether a common factor will ever be found in the mode of action of these diverse agents we still do not know.

The Long Latent Period; Its Bearing on the Problem of Causation.

In planning future researches into the causation of human tumours, it is of the utmost importance to appreciate fully that a long latent period commonly intervenes between the application of the carcinogenic stimulus and the eventual appearance of the tumour. Further, the stimulus may have ceased to act long before the appearance of the tumour. Thus, a carcinogenic hydrocarbon may be applied to the skin of mice for two or three months and then the application may be discontinued; the resulting tumours may not appear until a further six, nine, twelve months or more have elapsed—that is, a considerable part of the life span of the animals. So also in human carcinogenesis; the mule-spinner or the Joachimsthal miner may have retired from the offending occupation five, ten or fifteen years before his tumour appears; the fair-skinned farmer or sailor often does not develop his multiple actinic cancers until after many years of exposure, and perhaps after his retirement to an indoor life.

Clearly, then, it is usually futile to look for the causes of human tumours in the habits and occupations of the affected persons in the periods immediately preceding the appearance of their tumours. The tumour of today is often the resultant of stimuli applied ten, twenty, thirty and fifty years ago. Our medical histories of tumour patients are almost totally defective in this respect; detailed inquiry into the occupations and habits of the whole of the patient's previous life is never undertaken. Here is a great unexplored field of research, exploration of which by competent workers with a full knowledge of the problems involved must be undertaken if we are to sift out of man's complex environment those factors which may be carcinogenic for particular tissues. Incidentally, the same careful study and evaluation of the patient's environment, past as well as present, must be undertaken in order to unravel the causation of many other kinds of chronic disease—anæmias and other blood diseases, hepatic degenerations and cirrhoses, endocrine disorders, and chronic renal and arterial disease. A Herculean and highly complex task, no doubt; but then civilization and its ills is a complex subject.

The Mode of Origin of Tumours.

It is commonly assumed that a tumour starts from a single minute focus of tissue—some have said a single cell—and that it grows only by proliferation of the cells of that focus. The falsity of this view is clear, both from the findings of experimentalists and from the structure of young tumours (Willis, 1944). When a carcinogenic agent is applied to a tissue, it is clearly not applied to a single tiny focus, but to a considerable field of tissue of greater or less extent. When a tumour first appears, of course, it first appears at a particular spot; but its subsequent enlargement is often, not solely by proliferation of neoplastic cells, but also by spread of the neoplastic change to more of the surrounding tissue to which the original carcinogenic stimuli were applied. The field of potential neoplastic change is sometimes very extensive; for example, in the condition of polyposis of the colon, the entire colonic mucosa is potentially cancerous; some mammary cancers clearly arise in a widespread manner over much or all of the mammary tissue in one or both breasts; and the fair-skinned farmer in whom develop multiple keratoses and carcinomata of face and hands has the whole of the epidermis of these areas in an unstable, potentially cancerous state.

The phenomenon of multifocal or widespread cancerous change in a field of similarly predisposed tissue is of some practical importance to the surgeon. Post-operative recurrences are not always due to residues of tumour tissue left behind, but sometimes, as Thiersch long ago insisted, to further neoplastic transformation of the tissues of a potentially cancerous field, only part of which has been removed. Carcinoma of the vulva often affords clear examples of this kind of recurrence; the surgeon knows that purely local excision of a carcinomatous area in vulval leucoplakia is apt to be followed by further carcinomatous change in other areas, and that therefore complete vulvectomy is the only adequate surgical treatment. The same applies to carcinomatous change occurring in burn scars; once this has commenced at one part of the scar, other parts of the scar are likely to follow suit; so that the proper surgical treatment is, not merely local excision of an area of growth, but total removal of the whole scarred area.

Heredity in Human Cancer.

We have already noted that we must not directly apply to human pathology the results of close in-breeding of animals of high or low cancer incidence strains. Nevertheless, there are certain striking instances of the occasional occurrence of a strong inherited or familial predisposition to a particular kind of tumour. Such a predisposition is, like that obtained in closely in-bred animals, always for cancer of a particular organ or tissue, and not for cancer in general.

Thus the condition multiple polyposis of the large intestine may affect many or all of the members of a family, and may appear in several successive generations. In the affected individuals it almost always terminates during adolescence or early adult life in the development of carcinomata of the intestine, which are often multiple and may be numerous. These unfortunate people are not born with carcinoma, or indeed with polyposis, but with an unstable colonic mucosa which soon reacts in this abnormal neoplastic way to the ordinary stimuli of life which are innocuous to the normal person's intestine.

So also, patients with the rare skin disease *xeroderma pigmentosum* are born with a peculiarly abnormal susceptibility of the skin to the action of sunlight and other external stimuli. During childhood or adolescence they develop multiple, often very numerous, carcinomata of the epidermis of exposed parts.

The retinal tumours (retinoblastomata) of infancy and childhood afford some of the most striking instances of a familial and inherited predisposition. Not only may these tumours develop in many or all of the children in a family, but these may appear in one or both eyes at very early ages, not infrequently being already present at birth. Transmission of this peculiar genetic tendency through

several generations has been observed. An interesting recent review of the subject with discussion of its eugenic aspects has been written by Weller (1941).

The Possible Formation of Carcinogenic Substances in the Body.

The close chemical relationship between the carcinogenic hydrocarbons of the benzanthracene group and some naturally occurring biological substances, such as the bile acids and the sterols, has naturally led to speculations as to the possible formation of carcinogens in the tissues themselves. It is quite feasible that, in suitable pathological conditions, abnormal metabolic or degenerative products may include carcinogenic substances. I have already mentioned the possibility that this may occur in the contents of obstructed breast ducts, and it is not difficult to think of other possible instances. Perhaps in the gall-stones which are usually present in the cancerous gall-bladder a carcinogenic substance has been slowly generated; perhaps this has happened also in the smegma retained under the prepuce of the cancerous penis; perhaps the sebaceous contents of a cystic teratoma of the ovary in which carcinoma has supervened has developed carcinogenic properties; perhaps the proneness to malignant change following syphilis of the tongue or bilharzial infection of the bladder is due to carcinogenic metabolic products peculiar to those inflammations.

The research of the future will certainly include attempts to isolate pure carcinogenic substances from these and other conditions. While no such endogenous carcinogens have so far been identified, there is already substantial experimental evidence of their existence. For example, it has been found that suitable extracts of normal or of diseased livers are feebly carcinogenic (see Kleinenberg *et alii*, 1940), and that this property is more pronounced in extracts of livers already cancerous and in extracts of livers of races unusually liable to hepatic cancer—for example, the African Bantus (Des Ligneris, 1940; Hieger, 1940).

Some Research Suggestions.

Records and Statistics.

For reasons already given, our histories of patients suffering from tumours must be obtained in much greater detail with respect to previous occupations, habits and diet. Only by careful analysis of such information shall we be able to obtain pointers to hitherto unsuspected carcinogenic hazards in our industrial and domestic life.

At the same time, greater precision in the histological diagnosis of tumours must be attained. Let us recall that "cancer" embraces many different diseases, and therefore that for accurate statistical purposes the only figures really worthy of analysis are those based on diagnoses established by competent histopathologists. Ideally, not only tumours which the clinician or pathologist deems of doubtful nature, but all tumours removed surgically or discovered *post mortem*, should be identified microscopically. From my own experience, I can affirm that adoption of this practice will lead to many surprises; the "obvious" clinical or naked-eye diagnosis is not seldom refuted by the microscope. Those who believe that morbid anatomy and histology have become antiquated in cancer research are the sort of people who prefer straw to bricks for building purposes.

In an excellent paper entitled "Cancer Statistics as they Appear to a Pathologist", Wells (1927) has outlined the reasons for rejecting as valueless for statistical purposes the great bulk of cancer mortality figures. Few clinicians and statisticians adequately appreciate the extent of diagnostic error recorded on death certificates. I myself, from the Alfred Hospital records, can confirm the finding of Wells and other pathologists, that even in major city hospitals, with their highly competent staffs and every diagnostic facility, post-mortem examinations show that more than one-quarter of all cancer cases are misdiagnosed. The proportion of cases unrecognized or misdiagnosed in general practice must surely be much greater. Diagnostic error is, of course, greatest with regard to internal cancers; mammary, cutaneous, oral and uterine cancers are less subject to errors of diagnosis, but some mistakes occur even in these. Cancer statistics, then, are dangerous things in the hands of the unwary or of the prejudiced.

Carcinogens in Pathological Material.

By biological tests, and perhaps by physical and chemical tests, future research will have to determine whether or not carcinogenic substances are generated in the skin over-exposed to sunlight, in the stagnant contents of obstructed breast ducts, in the syphilitic tongue, in gall-stones, in retained smegma, or in the sebum of "dermoid" cysts. In prosecuting the search for such substances, we must recall that minute traces of carcinogenic hydrocarbons can evoke tumours, and therefore that carcinogens generated in the body itself may also be effective in minute quantities and may require special methods for their detection.

External Carcinogens.

The search for external carcinogens, as I have already indicated, has been prosecuted only within the last two decades. What has been achieved in that brief period augurs well for future progress in this field. Undoubtedly an increasing number of carcinogenic substances will be identified in the materials we handle, in the dusts and vapours we inhale, and in the foods, drinks and drugs we ingest.

As was to be expected, there has been more initial progress in the identification of carcinogenic agents externally applied to the skin than in the identification of those ingested or inhaled. Probably, indeed, we already know most of the external agents causing human cutaneous cancer. The task of identifying the effective agents in the air we breathe and the variable and complex mixtures we ingest is much more formidable. This will be a major task in future research into tumour causation.

In this connexion, I wish to advance a suggestion regarding alimentary cancers, which, though only speculative, is certainly plausible and worth thinking about. Cancers of the stomach and of the large intestine, though rare in all animals, are extremely common in man; cancer of the small intestine is very rare in man as well as in animals. These facts can be plausibly explained on the supposition that human alimentary cancer is largely due to ingested carcinogenic chemical substances. After a solid meal the stomach retains its contents for several hours, during which time a carcinogen present in the food would be applied to the mucous membrane. If such a carcinogen was, like many of the hydrocarbons, not affected chemically by the digestive process, and not absorbed, it would leave the stomach unaltered to enter the small intestine. Here, however, it would be diluted by the addition of the various digestive juices, and it would be hurried along through the length of the intestine, to the mucosa, to which it would be applied only transiently. In the large intestine, however, the absorption of water and the long retention of fæces would mean that our hypothetical carcinogen was again, as in the stomach, in contact with the mucous membrane for long periods and in a concentrated form.

From the comparative incidence and the distribution of alimentary cancers, I therefore strongly suspect that their main causes are ingested chemical substances. I would go even further in my speculations, and suggest that these substances may well include hydrocarbons of the kind discovered by Kennaway and his colleagues or some closely similar substances. Recall how Kennaway found that heating almost any organic matter to high temperatures would produce carcinogenic tars artificially; then reflect upon the possible changes produced in food by cooking and canning processes. Perhaps the amber colour acquired by fat used repeatedly for frying, as in the fish shops, or the beautiful brown colour on the surface of roasted baked foods, is not without its dangers. Future research will have to ascertain whether these denote changes analogous with those produced in Kennaway's artificial tars. If they do, it is not impossible that the main causes and the means of prevention of the commonest forms of internal malignant disease, the alimentary carcinomata, may ere long be made clear.

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NON-GONOCOCCAL URETHRITIS: CONSIDERATIONS OF ÆTIOLOGY; FINDINGS IN TWO CASES.

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IT is a common practice to regard all purulent urethral discharges from male patients as being gonococcal in origin and to regard the watery or colourless, mucoid type of discharge as insignificant. Hence, routine laboratory investigations have been mainly concerned in establishing a diagnosis of gonorrhœa, and they throw little light on the ætiology of the condition after this has been excluded. The assumption that the gonococcus frequently escapes detection, even by the most thorough laboratory procedures, has led to a great deal of attention being paid to improving existing laboratory techniques, with the result that the whole problem of urethritis has perhaps been focused unduly on the gonococcus, and comparatively little work has been done with other causes in view.

The problem has not, however, been entirely neglected. For many years a virus ætiology has been suspected by various German workers to account for certain types of urethritis, and in a number of instances a relationship between non-gonococcal urethritis and conjunctivitis of the newborn has been demonstrated. More recently, workers in America and Beveridge[1] in this country have isolated a pleuropneumonia-like organism from the male urethra, but further work on this organism will be necessary to assess its exact ætiological role.

Virus.

The virus diseases, for the main part, are characterized by the occurrence of inclusion bodies in cells of infected tissues. As early as 1909 inclusion bodies were demonstrated by Lindner[3] in epithelial cells in urethral smears from cases of urethritis. Halberstaedter and Prowazek,[2] in 1909 and 1910, and Heyman,[4] in 1910, found inclusions in epithelial cells from the genital tract of mothers whose babies had developed conjunctivitis shortly after birth. They also found inclusions in cases of conjunctivitis, in which gonococcal infection had been excluded by careful bacteriological examination. Inclusions resembling those found in inclusion blennorrhœa and trachoma have since been detected in urethral smears by a number of workers, and more recently Thygeson and Mengert[5] were able to demonstrate the virus of inclusion blennorrhœa in smears from the *cervix uteri* of mothers whose babies suffered from conjunctivitis; these smears were made ten to twelve days after delivery.

Also by animal inoculation, Fritsch, Hofstaetter and Lindner,[6] in 1910, indicated that the infection of the baby was derived from a genital disease of the mother. They found that the vaginal secretions of mothers of babies suffering from inclusion blennorrhœa were infectious in the eyes of baboons. They also produced a similar conjunctivitis with a gonococcus-free secretion obtained from male patients suffering from urethritis. The infection could be transmitted from one animal to another. Inclusion bodies were seen in conjunctival scrapings from infected animals. Thygeson,[7] Tilden and Gifford,[8] and Julianelle, Harrison and Lange[9] showed that secretions after passage through bacterial filters still retained their infectivity for men and animals, although in some instances this was diminished.

Thygeson and Mengert[10] recorded a case of interest, which provides strong evidence that the virus of inclusion blennorrhœa is located in the female *cervix uteri*. A gynæcologist, in performing a uterine dilatation and curettage, accidentally received a spurt of blood into his own eye, and six days later conjunctivitis developed. Microscopic examination of conjunctival scrapings revealed the presence of free initial and elementary bodies. This is one of a number of authenticated instances of accidental infections.

Braley[11] studied the changes in conjunctival and cervical tissues infected with the virus of inclusion blennorrhœa, and showed that inclusion bodies could be demonstrated in fixed sections. He pointed out that the virus was limited to a transitional zone of epithelium of the cervix, and this type of tissue resembled that infected in the conjunctiva. Cell inclusions, apparently, do not occur in the vaginal epithelium.

A non-trachomatous conjunctivitis with epithelial-cell inclusions, occurring in epidemics amongst bathers in public swimming pools, was first recognized by Huntemuller and Paderstein[12] in 1913. It is thought that urination whilst swimming is the principle means of dissemination of the virus. The cell inclusions, in this condition, are identical with those of inclusion conjunctivitis.

Also by filtration Thygeson[13] estimated the size of elementary bodies to be between 0·39μ and 0·15μ. By direct microscopic measurement the elementary bodies are estimated to be 0·2μ and 0·25μ in diameter. The small inclusions in Giemsa stained smears are bluish. Large inclusions made up predominantly of elementary bodies stain a bluish-red. There is a regular sequence of morphological development from a small form to a large form; it is estimated that this cycle takes about forty-eight hours. Morphologically, the inclusion bodies of inclusion blennorrhœa and so-called inclusion urethritis are no different from Halberstaedter-Prowazek inclusion bodies found in trachoma.

To date, attempts to cultivate the virus on the chorio-allantoic membrane and in tissue culture have been unsuccessful.

It has been stated by Anwyl-Davies and King[14] that urethritis is sometimes the primary manifestation of a lymphogranuloma infection. Numerous other instances have been given in which non-gonococcal urethritis was caused by the virus of *lymphogranuloma inguinale*. In this connexion it may be mentioned that there is a clinical entity which was first described by Waelch (1901), which is characterized by a scanty urethral discharge, a long incubation period and slightness of subjective and objective symptoms. Inclusions are present in epithelial cells. Organisms are not usually detected in uretheral smears. The diagnosis rests on the characteristic urethroscopic appearances. Greyish or greyish-yellow nodules are seen in a reddened mucous membrane, an appearance which is said to resemble that in trachomatous conjunctivitis. The feature of interest in this condition is the fact that a positive response to the Frei test results when patients suffering from *lymphogranuloma inguinale* are injected intradermally with urethral discharge from these patients. Bezency[15] suggests that this type of urethritis may be due to a filtrable organism akin to the virus of *lymphogranuloma inguinale*. However, the virus of Waelch urethritis does not produce meningo-encephalitis in mice as does the virus of *lymphogranuloma inguinale*. On this evidence there appears to be no relationship between the virus of inclusion blennorrhœa and that of *lymphogranuloma inguinale*.

This review tends to lay stress on positive results; but there have been many unsuccessful attempts to produce the disease in susceptible animals, and inclusion bodies have not been demonstrated in numerous instances. Whether the ætiology has been entirely different in other instances, or whether the technique has been at fault, remains to be determined. Unquestionably there are a number of clinical types of non-gonococcal urethritis varying from a mild, frequently unnoticed, anterior urethritis to a severe, purulent condition which often involves the posterior part of the urethra and the prostate, and it seems reasonable to assume that other causes may also be active.

To sum up, there seems little doubt that there is a virus which causes urethritis in the male, and that the reservoir of this infection is the genital tissues of the female, whence it may also be transmitted to the conjunctival sac of the newborn during passage through the birth canal.

Pleuropneumonia-like Organisms.

Beveridge[16] reported the isolation of a pleuropneumonia-like organism in four out of 24 cases of urethritis in the male. He described a sensitive method of isolation in semisolid serum agar. He also described morphological and cultural characteristics and gave results of serological investigations and animal inoculation. He suggested that a large series of cases of urethritis should be investigated before any ætiological role was ascribed to this group of organisms.

The pleuropneumonia-like organism was first isolated from human beings by Dienes and Smith,[17] in 1940, who have isolated this organism from 23 of 77 cervical swabbings, from one of eight vaginal swabbings, from three prostatic secretions, and from one of eight urethral discharges from men. It is interesting to note that a number of these patients from whom the organism was isolated, had pathological lesions—for example, chronic prostatitis, rheumatoid arthritis, polyarthritis, chronic cervicitis, tenosynovitis and chronic gonorrhœa. Dienes and Smith concluded from their findings that the pleuropneumonia-like organisms may live in the genital tract without causing obvious disease, and that the evidence strongly suggests that they are capable of acting as pathogenic agents alone, or in combination with other bacteria, to produce a clinical condition resembling gonorrhœa and associated complications. In this connexion it should be mentioned that the pleuropneumonia-like organism was first isolated from a culture of *Streptobacillis moniliformis*, and was for some time regarded as a symbiot of this organism. There is a possibility that it may occur in symbiosis with other organisms.

It will be noted that in the majority of instances the organism has been isolated from the cervix, and apparently only rarely from the male urethra.

The two cases reported in this paper were selected from a large number of cases of urethritis investigated over a period of twelve months along the lines suggested by previous workers. Gonorrhœa was excluded as far as possible by the following measures: (i) intensive search of urethral smears; (ii) attempted culture on CCY 10% human serum agar slopes (casein hydrolysate, casein tryptic digest, yeast extract—Gladstone and Fildes[18]); (iii) gonococcal complement fixation tests, performed at regular intervals; (iv) observance of the clinical response to sulphonamide or penicillin therapy, or to both.

Willis,[19] in 1942, suggested that sulphonamide therapy had caused the gonococcus to take on a new ultramicroscopic or an unrecognizable pleomorphic form. Observation of the organism in smears during treatment has shown, however, that either the gonococcus is sensitive to the drug and its disappearance coincides with clinical improvement or it is insensitive and persists, morphologically typical, in association with all signs of active disease.

On the other hand, it is recognized that in the course of penicillin therapy the gonococcus frequently exhibits pleomorphism; but this is a transitory change in the process of its elimination from the urethral exudate and presents no diagnostic pitfalls.

It is interesting to note that penicillin is not so effective in the treatment of non-gonococcal urethritis as in the treatment of primary acute gonococcal infections.

To detect infection with a virus the following routine procedures were adopted. (i) Giemsa and Castaneda stained urethral smears were examined for inclusion bodies. (ii) Urethral washings, serum and saline solution or serum and broth being used, were inoculated after passage through a gradocol membrane (800$\mu\mu$) onto the chorio-allantoic membrane of nine to twelve day developing chick embryos.

To isolate pleuropneumonia-like organisms, Beveridge's[20] suggestions were adopted in part. (i) The anterior part of the urethra was washed out with Turner's[21] "V.F." broth containing human serum (30%), and a portion of the unfiltered washings was inoculated into Turner's "V.F." broth containing human serum (30%), agar (0·3%) and sulphanilamide (250 milligrammes *per centum*). (ii) The washings after filtration through a gradocol membrane were inoculated into the same medium as Turner's "V.F." broth containing human serum (30%), agar (0·3%) and sulphanilamide (250 milligrammes *per centum*).

Reports of Cases.

The two cases of non-gonococcal urethritis reported in this paper are of particular interest in that cell inclusions were demonstrated in urethral smears, and a pleuropneumonia-like organism was also isolated from both patients.

Case I.—Sergeant K. gave a history of urethral discharge and slight burning on micturition two days prior to his admission to hospital. He had had intercourse with a "friend" on two occasions, fourteen and twenty-one days previously. He denied any prophylactic measures. There was no history of previous venereal infection.

On his admission to hospital he had a thick, yellowish urethral discharge. Microscopic examination of urethral smears revealed many pus cells and relatively few epithelial cells. No organisms were seen. However in Giemsa and Castaneda stained smears the cytoplasm of epithelial cells contained scattered small cocco-bacillary basophilic elementary bodies. Some of these bodies appeared to be extracellular. Few initial bodies were seen. A few colonies of diphtheroids were present on CCY blood agar plates after incubation for forty-eight hours in the presence of carbon dioxide (10%).

On the eighth day of his illness the anterior portion of the urethra was washed out with four or five mils of Turner's serum broth, and portion of this was passed through a gradocol membrane and inoculated (*a*) into Turner's "V.F." broth containing human serum (30%) and agar (0·5%), and (*b*) into the chorio-allantoic membrane of nine to twelve day chick embryos. Portion of the unfiltered broth was inoculated into the same medium as (*a*), containing sulphanilamide (250 milligrammes *per centum*). There was no growth in this medium after anaerobic and aerobic incubation for 10 days.

Sections of the chorio-allantoic membranes were made after the second and sixth passages. No specific lesions were seen. Eight days after his admission to hospital the patient was given 200,000 units of penicillin over a period of twenty-four hours. At this stage he had had no treatment while in hospital. After this course of penicillin treatment the urethral discharge persisted. Seven days later he was given a further 200,000 units of penicillin, and urethral irrigations with silver nitrate were commenced. Prostatic examination on the fourteenth day after the onset of the urethral discharge revealed an enlarged right lobe of a tense and tender prostate. The urethral discharge persisted. There was little change in the patient's condition, and seven days after the second course he was given 400,000 units of penicillin, shortly after which the urethral discharge disappeared. However, the prostatic fluid was packed with pus cells.

Approximately one month after his admission to hospital the patient complained of severe pain on micturition. He was pyrexial and confined to bed. The urine contained many pus cells and red blood cells. No organisms were seen in repeated examinations of prostatic smears. The prostate was enlarged and extremely tender. *Trichomonas vaginalis* was not detected in the prostatic fluid. The epithelial cells in the prostatic fluid were characterized by degenerative changes; this made the interpretation of large inclusion-like bodies difficult. Inclusions were seen, but they did not resemble those seen in urethral smears. The prostatic fluid was incubated in Turner's "V.F." broth containing human serum (30%), agar (0·3%) and sulphanilamide (250 milligrammes *per centum*), and a pleuropneumonia-like organism was subsequently recovered in pure culture. The primary culture was contaminated with staphylococci and diphtheroid organisms.

The patient made a slow recovery from his prostatic infection. A course of sulphathiazole was given after the third course of penicillin. He was discharged "cured" after fifty-six days in hospital. Intradermal injection of a saline suspension of the organism, heated for two hours at 60° C., caused an area of intense hyperæmia about 1·5 centimetres in diameter after forty-eight hours.

Neither the Kline test nor the gonococcal complement fixation test produced a reaction. The latter test was carried out by means of two techniques and repeated at intervals of one week (Thomson[22] and Price[23]). Urethroscopic examination revealed no unusual characteristics.

Case II.—Private J. gave a history of intercourse with a "friend" seven and eight days before his admission to hospital. He denied any prophylaxis. He had noticed a discharge and a slight irritation of the *glans penis* one day before his admission to hospital. He gave no history of previous venereal infection. His general health was good in spite of repeated attacks of asthma.

On his admission to hospital a profuse, thin, sero-purulent discharge was present. There was no enlargement of inguinal glands. He had a very small meatal orifice; consequently no urethroscopic examination was made. *Trichomonas vaginalis* was not detected in wet preparations of the urethral secretions. In Gram stained urethral smears numerous pus cells and a few epithelial cells were seen; no bacteria were found. In both Giemsa and Castaneda stained films, small cocco-bacillary basophilic inclusions were present in the cytoplasm of epithelial cells.

Three days after the onset of the urethral discharge the anterior portion of the urethra was washed out with four or five mils of Turner's "V.F." human serum broth, and a few drops of this washing were inoculated into Turner's "V.F." broth containing human serum (30%), agar (0·3%) and sulphanilamide (250 milligrammes *per centum*). The remainder was passed through a gradocol membrane, and portion of the filtrate was inoculated in Turner's "V.F." serum agar without sulphanilamide, and onto the chorio-allantoic membrane of nine to twelve day chick embryos. Urethral scrapings were inoculated onto CCY human serum agar plates in the presence of carbon dioxide (10%). A few colonies of diphtheroid organisms were obtained after incubation for seventy-two hours. After aerobic culture for five to seven days, tiny colonies were noted in the sulphanilamide-containing medium. These were subcultured into sulphanilamide-free medium and gave the typical colony appearances of pleuropneumonia-like organisms described by Beveridge. This organism has been subcultured about twenty times without difficulty. Sections were made of the chorio-allantoic membranes after the fourth and sixth passages. There were no lesions which could be regarded as specific. No cell inclusions were seen.

Three days after his admission to hospital the patient was given 200,000 units of penicillin, and four days later the urethral discharge disappeared. However, after prostatic massage the fluid contained clumps of pus cells. There were no symptoms referable to the prostate.

The Kline test failed to produce a reaction. The gonococcal complement fixation test produced no reaction by Thomson's technique and produced a "doubtful positive" reaction by Price's technique. However, the patient's serum was slightly anti-complementary, and no quantitative changes were found by tests made at intervals of one week while the patient was in hospital. Beveridge reported that the strain of pleuropneumonia-like organism isolated from this patient was not inhibited in medium containing 25 to 100 units of penicillin per ml. The Frei test, performed six weeks after his admission to hospital, failed to produce a reaction (antigen of doubtful potency). The patient reacted strongly to intradermal injections of a saline suspension of the pleuropneumonia-like organism. Subsequent attempts to cultivate the pleuropneumonia-like organism were unsuccessful. No cell inclusions were demonstrated at a stage of the disease when the urethral discharge was almost non-existent.

The patient made a slow recovery from what was apparently a low-grade prostatitis and was discharged after forty-nine days in hospital.

Discussion.

The clinical picture in both these cases of urethritis resembles that of acute gonorrhœa, and is unlike the majority of infections ascribed to a virus related to that of inclusion blennorrhœa. These are said to be rather mild and are usually sensitive to the sulphonamide drugs.

The gonococcus was not grown in culture nor detected in repeated urethral and prostatic smears from both these patients. There is not a single positive finding to suggest that Sergeant K. was suffering from gonorrhœa. All complement fixation tests carried out during the active and quiescent stages of the disease failed to produce a reaction. Little significance can be attached to the persistent weak reaction to the gonococcal complement fixation test, carried out by Price's technique, and there was no quantitative change from week to week. The serum was slightly anti-complementary. The test, carried out by Thomson's technique, produced no reaction.

The significant feature of these two cases of urethritis is the finding of epithelial cell inclusions. On the strength of experience in examining some hundreds of smears, it was considered that these were neither artefacts nor bacteria. The bovine strain of the pleuropneumonia-like organism does not give rise to cell inclusions. However, further observations on direct smears are necessary to determine whether or not the human strain of this organism is detectable in direct smears from the site of the lesion.

The skin sensitivity tests with the pleuropneumonia-like organism isolated from Private J. are of interest. The results were definite. Three normal controls gave no reaction. One other positive result was obtained in 13 cases of urethritis. There is not sufficient evidence to indicate the specificity of this reaction, and little importance can be attached to it at this stage.

The isolated observation of the *in vitro* resistance to penicillin is of some significance. Experience gained in the treatment of non-gonococcal urethritis indicates that penicillin therapy is not so effective in this condition as in the treatment of gonorrhœa.

To sum up, if past investigations and present findings are taken into consideration, three suggestions as to the ætiology of the disease in these two cases can be put forward: (*a*) that the cell inclusions are manifestations of an infection with a pleuropneumonia-like organism, which is responsible for the clinical condition; (*b*) that the urethritis is caused by a mixed infection with a virus and a pleuropneumonia-like organism; (*c*) that the condition is due to a virus infection, and the pleuropneumonia-like organism is a saprophyte or a low-grade excitant.

Direct evidence on these points is still incomplete, and for this reason various interesting side issues have not been discussed in this paper.

Summary.

1. Recent literature suggests that filterable viruses and pleuropneumonia-like organisms may be concerned in certain types of non-gonococcal urethritis.

2. Two illustrative cases of urethritis are described, in both of which intraepithelial inclusion bodies and pleuropneumonia-like organisms were identified in the urethral exudate.

3. The need for further research is emphasized.

Acknowledgements.

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Thanks are due to the Director-General of Medical Services for permission to publish this article.

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Reports of Cases.

A CASE OF SPRUE SYNDROME.

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SPRUE was originally the name given to a disease occurring in certain geographical areas in the tropics, characterized by stomatitis, glossitis, steatorrhœa, anæmia and emaciation. It

has often been termed "tropical sprue" to distinguish it from idiopathic steatorrhœa or non-tropical sprue. As pointed out by Snell,[12] Hurst[8] and others, these two diseases are really the same condition. The disease is commoner in the tropics because of its probable deficiency basis, and non-tropical sprue is correspondingly rarer. Snell,[12] in his excellent review of a series of cases of both diseases, points out that the main difference between the two conditions is that non-tropical sprue on the whole is more resistant to treatment than tropical sprue. The probable explanation is that the former occurs in areas where it is uncommon and is therefore not recognized until irreversible changes have taken place in the alimentary tract. There is a similar disease that occurs in children, cœliac disease. This may reasonably be included in the sprue syndrome, and presents its special features related to nutrition and growth on account of its occurrence in childhood. Hurst[8] has therefore included in the sprue syndrome the three diseases, tropical sprue, idiopathic steatorrhœa and cœliac disease.

The exact ætiology of the syndrome is unknown, but it is generally considered to be a deficiency disease, and is closely related to Addisonian anæmia on the one hand and to pellagra on the other. Castle *et alii*[1] in their work on this disease present some good evidence to support the theory that lack of the "extrinsic factor" in the diet is a cause, and that there is a lack of absorption of the "hæmopoietic principle" in the small bowel. The existence of an infective cause has been largely discounted.

If the above facts are borne in mind, the case reported may be regarded as an example of the sprue syndrome. Special reference will be made to the radiographic appearances of the small intestine as an aid to diagnosis and prognosis. Although these appearances have been described many times in the literature, they are not generally known. This method of examination should therefore be of help in arriving at a diagnosis in cases of this syndrome.

Clinical Record.

The patient, P.G.D.S., aged thirty-two years, was in good health, with no previous relevant illnesses, up till April, 1943. He had then spent nine months in Cairns, Queensland, a tropical area, and had received a well-balanced diet. His first symptoms were weakness and tiredness; these were followed shortly by ulceration of the mouth and tongue. He first came under medical observation in May, 1943, when he was treated expectantly as suffering from stomatitis. For the following six months the ulceration of the mouth and tongue became more severe and painful, his lack of energy became more pronounced, and he gradually lost one and a half stone in weight. At the same time he noticed the insidious onset of the passage of foul-smelling flatus *per rectum* and diarrhœa characterized by the passage of six to twelve pale, frothy, offensive stools per day. He complained of nausea with a varying fastidiousness of his appetite, and a particular aversion to meat. During this period his main symptom was recurring ulceration of the mouth in a more or less periodic fashion every three weeks. He was repeatedly investigated for a possible Vincent's infection with negative results, and local treatment had no lasting effect. During this time also a dry erythemato-squamous rash involving the dorsum of his left hand and left foot developed.

He was investigated in hospital at Townsville in October, 1943; he was found to have some degree of anæmia, the Kline test failed to produce a reaction with the blood, and the conclusion was drawn that the ulcers might have been produced mechanically by his finger nails, as he had a habit of biting his nails. He was discharged to duty. His symptoms continued as before, and he was readmitted to hospital for further investigation in December, 1943. He was then found to have macrocytic anæmia, a normal acid curve as revealed by a test meal examination, an excess of fat in the stools on microscopic examination, and a normal bone marrow picture. A diagnosis of pellagra was then made because of the associated skin condition. He was given "Anahæmin" (a liver preparation) parenterally and nicotinic acid by mouth. There was no reticulocyte response, but he began to feel better, he had more energy, his appetite improved and the ulcers in his mouth healed. There was no significant improvement in the blood picture; the erythrocytes averaged 3,200,000 per cubic millimetre, and the hæmoglobin value was eleven grammes *per centum*. After a month's treatment he was discharged to duty. His treatment as an out-patient was continued, but the ulceration of the mouth recurred.

In February, 1944, he was transferred to a base hospital in Sydney, a temperate climate. He then presented an aphthous type of ulceration of the tongue, the floor of the mouth and the inner side of the cheeks and lips. He had fatty diarrhœa, passing four to six stools per day, and he was slightly emaciated, but did not look unduly pale. There were small areas of eczema of an unpigmented erythemato-squamous appearance on the dorsa of the left hand and left foot. No abnormal clinical signs were found on examination of the nervous system. A blood count revealed that the erythrocytes numbered 3,100,000 per cubic millimetre, the hæmoglobin value was eleven grammes *per centum*, and the mean corpuscular volume was 103 cubic micromillimetres. The leucocytes were normal, and in the stained film considerable anisocytosis and macrocytosis were observed. Microscopic examination of the fæces revealed an excess of fatty acid crystals. The total fat in the dried fæces was 35%, of which 77% was split. The plasma calcium content was eleven milligrammes *per centum*. A glucose tolerance test after the oral administration of glucose revealed that the fasting level was 100 milligrammes *per centum*; for two hours there was a variation between 90 and 100 milligrammes *per centum* (Figure I). Serial X-ray examinations after a barium meal revealed delay in emptying of the stomach, a smooth appearance of the upper part of the jejunum, and collection of the barium in clumps in the lower parts of the small intestine (Figures II and III).

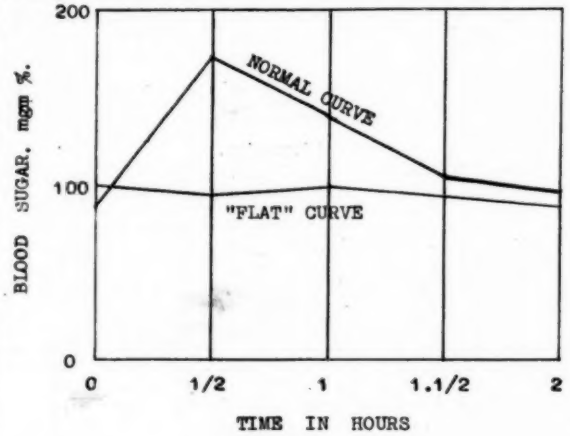

Figure I.

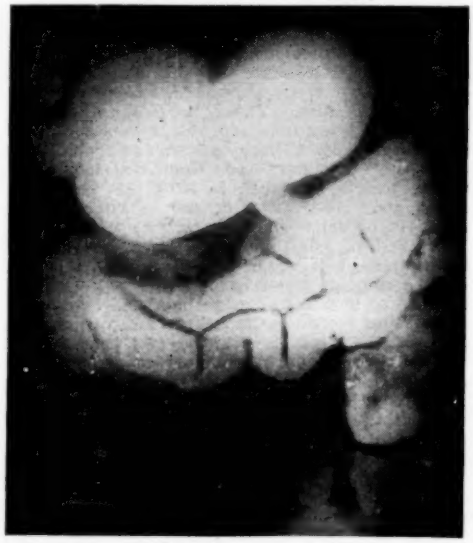

Figure II.

A diagnosis of sprue syndrome was then made. The patient was given a diet of about 2,200 Calories daily, the protein-carbohydrate-fat ratio being 1·0:1·3:0·3. The diet contained an adequate quantity of all vitamins with extra vitamin *B* complex in the form of "Marmite", four teaspoonfuls daily. At the same time he was given iron by mouth and "Campolon" (liver extract) parenterally in large doses. From the initiation of treatment at Townsville until June, 1944, he had gained one stone in weight, his appetite had been better and he had had more energy; but the blood picture had shown no material improvement, and the diarrhœa had if anything grown slightly worse. The eczema of the hand and foot gradually disappeared with no special treatment. The radiographic appearances of the small intestine were unchanged, and the result of analysis of the fæces fat was unchanged. His general condition had been stationary for two months.

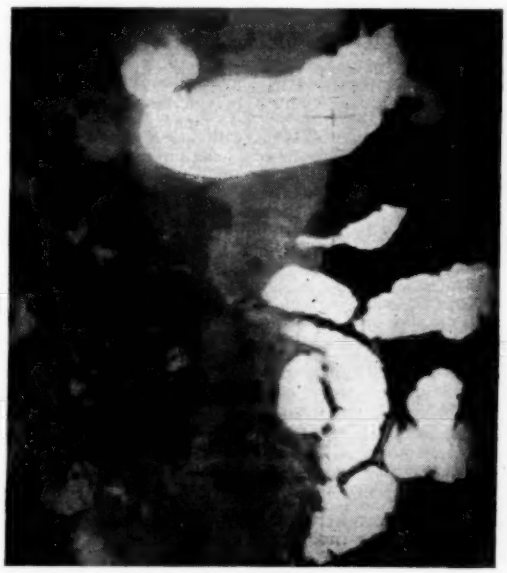

FIGURE III.

Discussion.

Diagnosis.

The diagnosis of sprue syndrome in this case was made on the general asthenia and emaciation, ulceration of the mouth, steatorrhœa, macrocytic anæmia, radiographic appearances of the small intestine, a "flat" curve response to the oral glucose tolerance test, and the course of the disease. The diagnosis of sprue syndrome was not made for nine months, mainly because the chief symptoms in the mind of the patient were ulceration of the mouth and weakness. Consequently, the first three diagnoses were Vincent's infection, aphthous ulcers and traumatic ulcers caused by finger nails. It was then found that he had a macrocytic anæmia without achlorhydria and in association with a rash on the left hand and left foot, and he was considered to be suffering from pellagra. This appeared reasonable, as he gave a good response when given nicotinic acid by mouth. However, in my opinion, the rash he had was not due to pellagra, either primary or secondary to sprue, as the rash was not symmetrical, nor did it affect other exposed areas, and I consider he had only the usual dysidrotic eczema common in the tropics. Kauffman and Smith[9] describe the characteristic cutaneous changes in sprue as rough, dry, loose and universally hyperpigmented macular eruptions. The patient states that he never had such a condition of the skin. A diagnosis of uncomplicated sprue syndrome was finally made on the characteristic fatty stools and confirmed by the points mentioned above.

Buccal Lesions.

Stomatitis and glossitis are usually associated with atrophy of the papillæ of the tongue, but in this case it was not pronounced, though the tongue had a slightly raw appearance.

Steatorrhœa.

The fatty diarrhœa is due to poor absorption of fatty acids and soaps from the small intestine. Hurst[6] states that all the necessary information can be obtained from a microscopic examination of the fæces stained by a saturated solution of copper sulphate. Neutral fat is unstained by this, but soap stains green and fatty acid can be easily identified as sheaves of colourless needle-like crystals. By this means it can be quickly decided whether the steatorrhœa is due to undigested fat, as in pancreatic insufficiency, or to an excess of fatty acid and soap, when the absorption is impaired. Hurst states that the cause of the impaired absorption in the syndrome is paralysis of the extension of the *muscularis mucosæ* into the villi; thus their pumping action in emptying the absorbed fat into the lacteals is stopped. If the diet is normal, the fat content of dried fæces in health is 12% to 33%, most of which is split. In this case, when a low fat diet was given, the total fat was 35%, of which 77% was split. If a normal diet is given, the total fat in the fæces in a case of steatorrhœa usually rises to 60% to 80%.

Radiographic Appearances.

The radiographic appearances of the small intestine in the condition were first described in 1934 by Snell and Camp.[13] In 1939 Kantor[8] divided the radiological diagnosis of the syndrome into four parts: (i) appearance of the small intestine, (ii) appearance of the colon, (iii) faint filling of the gall-bladder, and (iv) skeletal changes, such as dwarfism, deformity and osteoporosis.

No further comment will be made concerning the third and fourth factors. With regard to the second factor, the colon appears dilated, owing probably to fermentation of the sugars and redundancy of the colon.

With regard to the first factor, the three changes described in the small intestine are as follows: (*a*) *"Moulage"* sign in the upper part of the jejunum, so called because the opaque meal has the appearance of wax poured into a mould. It has been described elsewhere as the "lead pipe" appearance. This finding is diagnostic of steatorrhœa, and does not occur in any other condition that may cause a "deficiency pattern". It is also of use in prognosis, indicating a severe disturbance of the function of the jejunum, probably with permanent changes. (*b*) Dilatation. (*c*) Segmentation. This sign appears in the more distal portions of the small intestine, and is shown by the clumping together of the barium in separate areas. It is probably due to spasm.

Golden[3] refers to these radiographic appearances of the small intestine as the "deficiency pattern", which he describes under three headings, as follows:

1. Motility.
   - (*a*) Hypermotility in early stages.
   - (*b*) Hypertonus in early stages.
   - (*c*) Hypomotility in advanced stages.
   - (*d*) Dilatation, particularly in the jejunum in advanced stages.
   - (*e*) Abnormal segmentation, suggesting spasm, producing scattered separated boluses.
2. Mucous membrane.
   - (*a*) Coarsening of mucosal folds, especially in the duodenum and jejunum.
   - (*b*) Obliteration of mucosal folds in more advanced cases.
3. Flocculation of the barium shadow, producing a coarsely granular appearance.

Hypomotility of the stomach may also be present, causing a residue to be visible after six hours. Golden considers that in advanced cases the mucous membrane may not return to a normal condition, even though the X-ray appearances are normal. This is due to irreversible changes that take place in the mucosa. When the condition does resolve, the "deficiency pattern" is seen last in the middle third of the small intestine. Golden states that the causes of the "deficiency pattern" are vitamin *B* deficiency, emotional disturbances and œdema of the mucosa. Similar changes are seen in the newborn infant, before the nervous mechanism of the mucosa has developed.

Sussman and Wachtel[14] state that the "deficiency pattern" is due to œdema and infiltration of the submucosa, atrophy of the mucosa, damage to the musculature, and degeneration of the nerves in the intestine. Hurst,[6] on the other hand, is emphatic that there is no definite pathological change in the mucosa of the small intestine, and that the radiographic appearances are due to a paralysis of the *muscularis mucosæ*, the *valvulæ conniventes* thus being allowed to lie flat. He states that if an autopsy is performed in a case of sprue before post-mortem changes have had time to occur, or if special measures are taken to prevent such changes, then the mucosa of the alimentary tract is

entirely normal. He therefore regards the radiographic appearances and the inability to absorb the products of fat digestion as a functional abnormality of the small intestine, the exact cause of which has not been proved. Simultaneously with the clinical recovery of the patient the X-ray appearances return to normal. To support this theory, Hurst *et alii*[7] report a case of the sprue syndrome due to obstruction of the mesenteric lymphatics by a chronic tuberculous process. In their case no abnormality of the intestinal mucosa was found radiographically. Similar obstruction can be caused by Hodgkin's disease and lymphosarcoma. Most of the radiographic characteristics of the sprue syndrome, as it affects the small intestine, were illustrated by the reported case, and can be seen in the skiagrams (Figures I, II and III). These contrast noticeably with the normal pattern, reproduced for comparison (Figure IV).

Figure IV.

Glucose Tolerance.

The oral glucose tolerance curve is characteristically low or "flat", as is well illustrated in the reported case. By low is meant that the highest point on the curve is not greater than forty milligrammes *per centum* above the fasting level. The reasons for this type of curve, as stated by Lepore,[10] are as follows:

1. The rate of absorption is diminished, owing to the œdematous and atrophied condition of the intestinal wall. The total quantity absorbed is probably normal, as the hypomotility of the intestine compensates for the slow absorption.

2. The rate of removal of sugar from the blood is normal or slightly increased, as is shown by an intravenous glucose tolerance test. However, Tunbridge and Allibone[13] found that when an intravenous glucose tolerance test is made, the glucose tolerance in cases of sprue is normal or slightly diminished. They did not recommend the test as a routine because it was not very helpful, and in fifteen cases they had complications as a result of the intravenous injection of glucose in concentrated solution in a total of 132 tests.

3. The diet used in the treatment of sprue is rich in carbohydrate and low in fat, and as shown by Himsworth,[3][4] this in itself will cause the result of glucose tolerance tests to be a low curve. The oral glucose tolerance test is a useful confirmatory test, but not a diagnostic test in the sprue syndrome.

Treatment.

Treatment in this case was on straightforward lines, as already indicated. In a perusal of the literature there appears to be a variation of opinion as to which of the three—liver therapy, the exhibition of vitamin *B* complex, or a diet poor in fat—is the most important. Castle *et alii*[1] consider liver therapy the most important. Manson-Bahr[11] considers lack of nicotinic acid the probable cause and therefore recommends this line of treatment, though he states that it is not of benefit in ideopathic steatorrhœa, which he considers a separate disease. Hughes,[5] who gives an excellent review of the treatment, considers diet of the first importance to control the steatorrhœa and gaseous distension. He uses a protein-carbohydrate-fat ratio of 1·0:1·3:0·3. Liver therapy he also considers important; but does not lay great stress on the value of vitamin *B*.

As there is a difference of opinion as to treatment, so there is a difference of opinion as to the prognosis. Here again it appears to be largely due to variations in terminology and the types of cases met under different conditions. On the whole, in cases in which the diagnosis is made early and early treatment is instituted, response is rapid, whereas in those in which the lesion progresses to possibly irreversible changes in the intestinal mucosa and the "*moulage*" sign or "lead pipe" appearance of the jejunum, the response is usually slow, and recovery may not be complete. This is the position in the present case, and time seems to be bearing out the latter conditions with regard to the prognosis.

Summary.

1. A case of sprue syndrome is reported.

2. The diagnosis was made on the following points: (*a*) general asthenia and emaciation, (*b*) ulceration of the mouth, (*c*) fatty diarrhœa, (*d*) macrocytic anæmia, (*e*) "flat" curve result of the oral glucose tolerance test, (*f*) "deficiency pattern" of the small intestine, (*g*) course of the disease.

3. The syndrome is discussed with special reference to the radiographic appearances of the small intestine.

Acknowledgements.

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The Medical Journal of Australia

SATURDAY, APRIL 14, 1945.

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THE PROBLEM OF CHANGING FOOD HABITS.

In all parts of the civilized world today there will be found departures from pre-war diet determined by that sternest of masters, necessity. In more than one country the question has been voiced whether when peace returns there will be any permanent alteration in food habits arising from the conditions which war imposed. One small section of this query can be readily answered, namely, that the prohibitions of wartime will be gladly repealed once the chance is given; Britons will exult once more in white bread, despite the expostulations of nutritional publicists, and will import, as lavishly as their depleted purses will permit, fruits from Mediterranean orchards and gardens; Australians will give Canadian salmon, Scotch herring and Norwegian sild a quite ecstatic welcome. There are, however, possibilities of changes in eating which lessons learned in years of stress have inculcated, but the problem is enormously complicated by the fact that food is not purchased and eaten according to physiological precepts unless by a few cranks whose hypotheses are invariably wrong. All sorts of cross currents come into operation—price, pleasure, accessibility, tradition, agronomy, social snobbery, manners, customs and usages. In the United States the inquiry will demand a more difficult analysis than in Australia, for in that country, notwithstanding a highly organized system of transport through railway reticulation and extended waterways which might be expected to yield uniformity of food distribution, wide diversities will be found which have cultural or racial foundations detached from nutritional theory. Czech communities retain a tradition of high-glass gardening, and in consequence vegetables form a large proportion of their diet. In Puritan households food is used for rewards and punishments, and it is interesting to hear the fear expressed that the giving of emergency tickets to children may to some extent undermine parental authority. In southern States personal freedom is permitted to a degree distasteful in the northern States, for children's likes and dislikes are treated seriously and so a family meal may demand separate catering for each member. There has recently been published in Washington a bulletin of the National Research Council embodying a report of the Committee on Food Habits and giving evidence of a serious determination to apply scientific methods to the problems of national nutrition.[1] British efforts in the same direction are not so highly systematized, but aim at a similar objective. It was only to be expected that in countries with Anglo-Saxon traditions of liberty protests against dietary regimentation should have arisen. An editorial in *The Journal of the American Medical Association* for September 23, 1944, begins: "Somebody is always trying to change the eating habits of the American people. Sometimes the stimulus comes from a food faddist who has made up his or her mind that health lies in abstinence from meat or acid fruits or eggs or some other food that has been for years eaten by great numbers of people. Sometimes the urge comes from an agency like the American Meat Institute, the National Confectioners' Association or the manufacturers of cereals or of dairy products or the bakers of bread, telling us that we ought to eat more of their particular products. Associated with these campaigns are the promulgations of groups of scientists or nutritional authorities who want everybody to be familiar with the vitamin, mineral, protein, carbohydrate and fat content of everything they eat and to eat strictly according to formula." The editorial ends, "as long as our civilization continues to be based on the family, food habits are going to control eating", but it expresses the opinion that there will be improvements chiefly in the feeding of children, in the regulated enrichment of existing foods and in a greater interest in making food attractive to eye and palate. In England a spirited protest has been uttered by Lord Horder against procrustean food standards. "We should teach a little less than we think we know rather than strain the few facts of which we seem certain, to explain conditions which are complex and probably result from more factors than the few that have been revealed to us."[2] F. Le Gros Clark has also entered the lists on the side of Lord Horder and complains that we are looking on food habits as a health problem; we have almost changed milk from a beverage into a medicine.[3] He feels that if propaganda is to be conducted successfully this should begin in the school canteen aided by committees of parents, for this is the point at which social preferences are most readily influenced.

What changes in national nutrition are likely to arise in post-war Australia? It is to be hoped that the reckless waste of good food, all too obvious before the war, will be moderated; one does not wish to see the ultra-thrifty ways of the French housewife develop in Australia, and there is little possibility that they will arise, but some check on senseless waste will be timely. The classification of animal foods into those requiring coupons for their purchase and those not has already, so those in the butchering business tell us, led to a greater appreciation of the small meats and to a reduction of the rather foolish prejudice against what was unfortunately called offal. As is well known today in nutritional circles, liver, kidney, heart and sweet-

[1] "The Problem of Changing Food Habits: Report of the Committee on Food Habits, 1941-1943", *Bulletin of the National Research Council*, Number 108, page 177.
[2] *The Lancet*, July 8, 1944, page 53.
[3] *The Lancet, loco citato.*

bread have some important ingredients such as vitamins in greater amounts than flesh, and so are valuable adjuncts to human diet. This is all for the good and may be expected to remain. It is also possible that the art of cooking will undergo some betterment as a result of our restricted inventory of foodstuffs, though in antagonism to this is the great extension of delicatessen shops which provide already cooked viands, especially meats. There is assuredly a promising field for improvement in the teaching of cookery, and it is here that the school can do a signal service, provided the teachers are qualified for the task, which too often they are not. It is a sad reflection on our lack of interest in this vital aspect of nutrition that whilst Australia in the last thirty years has made notable advances in the quality of bacon, ham, vintage wines, raisins, sultanas, citrus and other fruits and savoury cheeses, there has been no real improvement in the art of cookery. Here is a chance for a reform which will not antagonize any section of the community. The indications happily point to an awakening of interest. One of the lessons learned by Britain in war is certain to be permanent, and that is the attractive presentation of the potato on the table. In a series of competitive cooking tests carried out in England the skill of various refugees in "making the potato a poem", as Lord Woolton humorously put it, came as a surprise to professional chefs as well as to housewives. We might well have some of this instruction in Australia. A similar competition on the many ways of preparing rabbit might easily advance our dietary standard. Then, too, it is to be sincerely hoped that the promised reorganization of the fishing industry will give the average Australian some approximation to British consumption; even if it were only one-half, the change would be revolutionary.

There is assuredly room for reform and improvement in food habits, but those who would act as advisers should walk warily. Considerations overlooked by the dietitian may be vital with those to whom the proselytism is addressed, and the teacher should understand human nature as well as the physiology of food. An unbalanced diet can do harm, but an unbalanced propaganda can do more.

Current Comment.

THE USE OF FLUORESCEIN IN THE INVESTIGATION OF PERIPHERAL VASCULAR DISEASE.

It is interesting to reflect on the great number of clinical observations made daily by doctors on the peripheral capillary circulation. The researches of Krogh and others on the subject stimulated clinicians as well as physiologists, and many other investigators since, notably Lewis and his school, have kept that interest alive. In the last few years fluorescein has been found to provide a valuable method for research into the diagnosis and prognosis of peripheral vascular disease. K. Lange and L. J. Boyd have done a considerable amount of original work on the subject and have now brought their work closer to the clinical field.[1] Fluorescein, originally used for physiological studies on the eye by Ehrlich and familiar in its common ophthalmological use, has been found to be readily detectable in the surface capillaries by a beam of ultra-violet light. As its name indicates, the drug converts ultra-violet rays of an appropriate wave-length to rays in the yellow-green region of the spectrum. Further, it is most fluorescent when exposed to rays of a wave-length intermediate between those of visible violet light and those capable of causing erythema. Lange and Boyd have found that by using a mercury vapour lamp with appropriate filtration, visual observation may be made of fluorescence on the skin or mucous membranes after fluorescein has been introduced into the circulation. For purposes of accurate research Lange and his co-workers have employed a photo-electric cell which permits actual measurements to be made of the concentration of the drug in any accessible vascular area. This device, the "dermofluorometer", is, as the authors justly remark, merely a refinement, but some of the findings of the simpler visual method are interesting, and suggest a possible occasional clinical value. Fluorescein does not appear to be toxic in the small doses used, and is readily excreted, though the rate of excretion is lowered somewhat if the renal function be lowered, as might be expected. Certain physiological experiments were carried out to clear up points connected with circulation times and concentration of filtrates, but of greater immediate interest are the clinical results. A series of nine patients with acute embolism of the legs was examined, and it was found possible to define the lowest safe level for amputation as far as the skin was concerned, and also to decide at once whether the collateral circulation promised to be free enough to make operation unnecessary. In some of the cases a block of the sympathetic chain was performed after the fluorescein test in order to exclude the possible fallacy of vasospasm. The authors found no difficulty in mapping out the vascular areas by their colour, and the lines of demarcation between fluorescent and non-fluorescent zones were quite distinct. Thrombotic occlusions of vessels were also found to be suitable conditions for the application of this prognostic test. Some help was also obtained in cases of arteriosclerosis where small peripheral areas of gangrene caused uncertainty concerning the viability of neighbouring tissues. It is also claimed that it is possible by this test to assess the outlook for healing and for skin grafting in ulcers of the leg.

Lange and Boyd have made extensive investigations on the peripheral circulation with fluorescein, even extending their observations to frost bite. It does not seem likely that the fluorescein test will have a wide field of application, but it is one of those applications of physiological principles to clinical medicine which is stimulating in that it sets up a possible standard of measurement in some important vascular conditions. Year by year the pressure on pre-clinical teachers tends to increase their remoteness from the clinical teachers, but we must hope that in the future more and more clinical teachers will bring to their task a practical interest in the application of physiological method.

[1] *Archives of Internal Medicine*, September, 1944.

INTRAVENOUS ADMINISTRATION OF FLUIDS IN THE TREATMENT OF ACUTE INFECTIVE STATES.

At first sight it might appear that no reader of an Australian medical journal would be interested in Rocky Mountain spotted fever. But this disease is a rickettsial infection and typhus is of considerable interest to Australian practitioners. This is not merely because patients from the south-west Pacific area suffering from mite-borne typhus have been observed and treated in military hospitals on the mainland, for it must be remembered that the so-called scrub typhus is endemic in certain parts of Queensland, and flea-borne typhus is occasionally seen in other parts of Australia. G. T. Harrell, W. Venning and W. A. Wolff have published an article on the treatment of Rocky Mountain spotted fever with particular reference to the intravenous administration of fluids.[1] They point out that there is no specific treatment as yet for these rickettsial infections and that disappointment has followed the use of chemotherapy up to the present time.

[1] *The Journal of the American Medical Association*, December 9, 1944.

Even antiserum has been found in the experiments so far conducted to be of little avail except perhaps in the first few days of infection. This should not surprise us when we recall that the rickettsiæ are intranuclear in their location. Harrell, Venning and Wolff state that "poorly directed or unwisely chosen parenteral supportive therapy may prove harmful". Experienced observers in the Pacific war zones will agree with this observation. The real point at issue is the criteria by which we may judge the advisability or even the peril of the parenteral use of fluids. Several case histories are given by these authors in which we may trace the well-known sequence of severe toxic disease, prolonged pyrexia, falling blood pressure only temporarily elevated by intravenous administration of fluids, generalized œdema and associated hypoproteinæmia. Harrell and his colleagues point out how the initial improvement after saline infusions may be explained, that is, by replacement of salt lost in sweat and of fluid loss, and they state that the subsequent worsening of the patient's condition was avoided by following the indication of reduced blood proteins and giving blood or plasma. It is to be regretted that the rate of the fluid infusions is not emphasized in this paper. A study of the details of treatment indicates care in this regard: one patient, for example, was given 1,500 cubic centimetres of plasma over a period of nine hours.

In discussing the whole question, Harrell, Venning and Wolff do not agree that the œdema is due to myocardial or renal failure, but consider that it follows hypoproteinæmia which in its turn is due to endothelial damage, a common feature of rickettsial infections. Large amounts of crystalloid solutions may actually aggravate the situation if given in these circumstances. These writers call the initial period of toxæmia a state of "medical shock" and believe further that the malign reputation of intravenously administered fluids in this condition is due to action delayed for too long. If anything is to be done in the way of supporting treatment, they contend, it must be done early before the vascular changes become irreversible. Not only are serum proteins reduced in these infections, but there is also evidence of great protein destruction, and thus to wait till general œdema sounds a belated warning is to wait too long.

A. E. F. Shaw and A. Daly Smith recently made a plea in these pages for the use of biochemical methods in the control of parenteral fluid therapy, and H. H. Kretchman described technical methods suitable for field work and discussed the principles involved.[1] These articles all state emphatically the necessity for assessing the physiological needs of these patients, and for basing fluid therapy on correct understanding and adequate investigation. To these injunctions we may add the admonitions of Marriott and Kekwick and other authorities on the safe rates at which transfusions may be given to persons seriously ill with debilitating disease. Although the actual clinical problem discussed here is really the adjuvant treatment of typhus fever, the principles apply also to other infective and toxic states. It must surely be accepted that peripheral circulatory failure is an expression of toxic vascular damage. The direct counter to this danger we do not possess in many cases, but where reasonable indications exist for supplying actual deficiencies in the body fluids, notably those of salt and of serum protein, it is justifiable to try with caution to follow such indications. It is important, however, to avoid such circulatory overloading as may lead to unhappy results.

RUPTURE OF THE HEART.

On previous occasions reference has been made in these columns to coronary occlusion and particularly to the ultimate prognosis in that all too common condition. It has been computed that something like 50% of patients who suffer from acute coronary occlusion die during the early and acute stage of the condition. Interesting studies have been made of the fate of persons who survive the initial attack, and it has been shown that the outlook is not so gloomy as has sometimes been thought. Of those who do not survive the initial occlusion some may die of cardiac rupture. In a recent study of rupture of the heart in myocardial infarction, S. Friedman and P. D. White[1] quote findings of H. S. Martland, who in 1940 found rupture of the myocardium to be the cause of the death of 42 (2·1%) of 2,000 persons who died suddenly. All of the 2,000 persons were over ten years of age and most of them were between forty and sixty-five years of age. In the series of 2,000 cases coronary occlusion with thrombosis was present in 304 cases, coronary occlusion without thrombosis was present in 314 cases and aneurysm of the left ventricle in 59. They also mention a study by H. A. Edmondson and H. J. Hoxie, who reported that among 25,000 post-mortem examinations between the years 1924 and 1941 there were 865 cases of unhealed myocardial infarction and that in 72 or 8% of these cardiac rupture had occurred.

Friedman and White state that one of the reasons for their having undertaken their study was the fact that W. W. Jetter and White had discovered a high incidence of rupture of the heart among patients in mental hospitals. Jetter and White's findings are published in the same journal as Friedman and White's. In the present instance it will be advisable to consider Friedman and White's findings first. Their series comprised 2,967 autopsies performed at the Massachusetts General Hospital. Among these 270 cases of myocardial infection were found and analysed. In 105 instances the myocardial infarction was recent and in the remaining 165 cases old coronary occlusion with healed infarction was found. In the latter group many ventricular aneurysms were found, but not one rupture had taken place. All the 105 cases of acute infarction had occurred within ten days of death, and in ten of them the immediate cause of death was rupture of the ventricle with tamponade from hæmopericardium. The average age of the ten patients was 65·7 years; seven were males and three were females. Death always occurred rapidly after the rupture. It is interesting to note that in two of the ten cases there was no history of previous cardiac malady. In five cases there was a history of *angina pectoris*, varying in length from two and a half weeks to five years; in two of these cases hypertension was present. In two cases there was a history of hypertension alone; in one of these it was "slight". In one case no statement is made about the previous history.

Turning to Jetter and White's article, we find that in a series of 115 consecutive autopsies of patients who died suddenly or unexpectedly at mental hospitals in Massachusetts, there were 22 cases of acute myocardial infarction; in sixteen of these cardiac tamponade due to rupture of the heart wall at the site of a recent infarct was found. In the same series a healed infarct was found in 25 cases, but no rupture occurred among these. The average age of the patients whose hearts ruptured was 66·5 years. Ten patients were males and six were females. Fourteen of the sixteen patients had a history of moderate to severe hypertension; in one case there was a family history of *angina pectoris*. The occurrence of *angina pectoris* in these patients cannot be determined because psychotic patients were found not to complain in most instances even though they were desperately ill. This is particularly true of patients who have deteriorated intellectually, and intellectual deterioration was a prominent feature in these patients. Ten of the sixteen patients were ambulatory and in apparent good health when they suddenly collapsed; four had complained mildly and two were incapacitated for twelve hours before death. In no case was an ante-mortem diagnosis of myocardial infarction or cardiac rupture made.

These papers contain valuable information for the general physician; they also emphasize the difficulties of officers in mental hospitals who often have to make a diagnosis from objective findings alone.

[1] The Medical Journal of Australia, September 16, 1944.

[1] *Annals of Internal Medicine*, November, 1944.

Abstracts from Medical Literature.

SURGERY.

Wound Healing.

R. H. Williams and G. W. Bissell (*Archives of Surgery*, October, 1944) have studied the effect of vitamins *A*, *C*, *D* and *E*, thiamin hydrochloride, nicotinic acid, riboflavin, calcium pantothenate, pyridoxine, biotin, hydrosulphosol, biodyne, urea-sulphathiazole ointment, amino acids, adenosine, liver extract cod liver oil, a "vitamin mixture" and sesame oil. The effect of sulphamerazine in conjunction with most of these substances was also tried. The experiments were conducted on uniform sized wounds in rats, and the substances were applied locally to the wounds. Four groups of rats were used and there were differences in the conditions of each group. No definite benefits were observed from the use of any of these substances as judged by frequent observations of the wounds, their strength and the microscopic changes.

Mesenteric Vascular Occlusion.

B. J. Ficarra (*The American Journal of Surgery*, November, 1944) reports fifteen new cases of mesenteric vascular occlusion, bringing the total reported cases to 569, with 35 recoveries. The author points out that occlusion may be arterial or venous and may affect the superior or inferior mesenteric vessels. In some a combination of these divisions is encountered. The cause of the occlusion is either embolism or thrombosis. Embolism is usually due to preexisting cardiac disease. Thrombosis in arteries follows vascular degeneration; venous thrombosis usually results from the extension of an infective process from some part of the area drained by the portal system. The author discusses the diagnostic features of the conditions. No pathognomonic sign or symptom is available, but the condition should always be considered in elderly patients with acute abdominal conditions. Pain is almost always present and may be cramp-like and constant or intermittent. Vomiting occurs later, and is usually present. Blood in the vomitus or stools is infrequent. On examination of the abdomen, tenderness, rigidity and distension were commonly noted, although the author was struck by the association of moderate tenderness with apparently intense pain. Audible peristalsis was almost always diminished. Leucocytosis occurs when incipient gangrene is present, and the leucocyte count is often as high as 30,000 cells per cubic millimetre. In the differential diagnosis acute intestinal obstruction, strangulation of bowel, acute pancreatitis and perforated peptic ulcer should be considered. Conservative therapy is fallacious and surgical resection of the involved loops beyond the areas of œdema affords the only hope of cure.

Penicillin in Chronic Osteomyelitis.

In view of the accepted position of penicillin as the most effective therapeutic agent for the treatment of staphylococcal infections, D. G. Anderson, L. G. Howard and C. H. Rammelkamp (*Archives of Surgery*, October, 1944) present a critical study of forty cases. The patients ranged from fourteen to seventy-four years of age. The duration of the disease varied from two months to forty-nine years. Most of the patients had already been treated with sulphonamide drugs without benefit. In carrying out surgical procedures it is essential to remember that a sequestrum has no blood supply, that an osteomyelitic cavity has a very poor blood supply, and that soft tissue scars and sinuses also have impaired blood supply, and so penicillin cannot be effective by that route. Attempts to overcome these difficulties were made by excising sinuses and scar tissue and granulations. Cavities were exposed and curetted. By closing in the edges and applying copious dressings, the operative area was made a relatively closed system, and the penicillin was injected into the area by means of catheters suitably placed. By this means and the systemic treatment it was possible to maintain a high concentration of the drug at the site where it was most needed. Additional doses were given by catheters every twelve hours. The dose was progressively reduced so that after the fifth postoperative day the patient was not receiving more than one cubic centimetre every twelve hours through any one catheter. Blood cultures were attempted, and in four cases of bacteriæmia the media were sterile after one to five days. The authors are satisfied that in a high percentage of cases penicillin arrests the infection and allows healing of both bone and soft tissue. The failures were due to development of resistance to penicillin by the organism. It is not clear how this untoward event can be prevented. The patients were observed for a year afterwards, and in 70% of cases there were no symptoms or signs of active infection.

Acute Starvation following Operation or Injury.

Robert Elman (*Annals of Surgery*, September, 1944) discusses acute starvation in surgery. When a healthy individual sustains a serious injury or undergoes a serious operation, starvation nearly always ensues. Starvation is described as deprivation of an organism of any or all of the elements necessary to its nutrition. These are water, salt, protein, fat, carbohydrate and vitamins. Apart from lack of intake there is toxic destruction of protein which may cause protein depletion even with full diet. The manifestations are loss of weight, anorexia, œdema especially of the gastric mucosa, lowered resistance to infection, hypoproteinæmia as shown by plasma analysis, and dehydration. It must be remembered that hypoproteinæmia may be masked by dehydration or hyperglobulinæmia. The author utters a warning against the vogue of orange juice which contains only carbohydrate and vitamin *C*, but is entirely deficient in salt and protein and leads to protein and electrolyte deficiency. Broth is a good source of salt, but often very deficient in protein. Milk suffers from high water content. Nitrogen balance cannot be achieved by the administration of protein alone. It is possible to maintain nitrogen balance by injecting intravenously glucose and hydrolyzed protein in equal parts, the caloric requirements being met by the fat. The author stresses the duty of surgeons to prevent acute starvation rather than to cure the effects. Adequate nutrition must be provided from the first by the oral or parenteral route. The caloric needs may be temporarily sacrificed provided an adequate protein intake is assured.

Plasma Cell Mastitis.

W. H. Parsons, J. C. Henthorne and R. L. Clark (*Archives of Surgery*, August, 1944) call attention again to the condition described as plasma cell mastitis. This condition was first described under this name in 1933 by Adair. It appears to be identical with a condition previously described in the German literature as *mastitis obliterans*, and in other quarters as pseudotuberculosis of the breast. Its importance lies mainly in the fact that it may be confused clinically with carcinoma of the breast. It is characterized by a unilateral painless tumour in the breasts of parous women. Mild signs of inflammation are sometimes present in the developing stage of the disease, but usually any tenderness passes off and it is at this stage that the resemblance to carcinoma may confuse the diagnosis. The lump is not tender. There are often retraction of the nipple and fixation to the skin with orange skin dimpling. Axillary glands are likely to be enlarged. There may be a watery or creamy discharge from the nipple. On section, the lesion appears to the naked eye as a yellowish brown discoloration of the mammary tissue, often associated with the formation of an abscess. The contents of the abscess and of the contiguous ducts are puriform or butter-like. The main histological features are ulceration of the epithelial duct lining which is replaced by granulation tissue, the formation of foreign body giant cells, and periductal collections of plasma cells and other leucocytes. Other features include areas containing sheaves of fatty acid crystals, foamy histiocytes and droplets of fat within the plasma cells. The authors regard the condition as a periductal inflammatory reaction caused by the extravasation of material high in lipid content from the ducts into the periductal fibrous tissue.

Carotid Ligation for Intracranial Aneurysm.

Lambert Rogers (*The British Journal of Surgery*, October, 1944) reports a case of carotid ligation for intracranial aneurysm. Before ligation, the effects of occlusion of the vessel were studied by electroencephalography. The author briefly discusses the danger of hemiplegia, even in young subjects, after carotid ligation in cases of saccular intracranial aneurysm. For twenty-three days before operation digital compression of the common carotid artery was practised for periods increasing from five to twenty minutes daily. The common carotid artery was then exposed under local anæsthesia and temporarily occluded by means of tape and silk ligatures. Dynamometer readings were taken every three minutes from both hands over a period of ninety minutes, and encephalograms were also taken. The homolateral hemisphere showed slightly more prominent normal rhythm than the contralateral, but always within physiological limits. The asymmetry was less marked in the later than in the earlier electroencephalograms. As neither

these nor the dynamometer readings suggested any serious impairment of cerebral function, the vessel was secured in two places with silk ligatures and divided. The symptoms (pain, impaired vision and ophthalmoplegia) were relieved, and hemiplegia did not ensue. An electroencephalogram taken three weeks later showed all rhythms within the normal frequency band. The author could find no previous record of electroencephalography having been employed in the study of carotid occlusion, and believes that such an investigation may prove useful in future cases.

Perirenal Insufflation.

F. L. SENGER AND J. J. BOTLONE (*The American Journal of Surgery*, November, 1944) discuss the radiographic examination of the kidneys after air insufflation of the perirenal space. In 175 consecutive investigations of this type much useful information was gained, and complications were infrequent and minor. The method, in which the use of an artificial pneumothorax machine is recommended, is described in some detail. Although they oppose the indiscriminate use of air insufflation, the authors consider that there should be no hesitation in employing it where it is indicated.

Defunctionalizing the Colon.

EDGAR F. BERMAN (*Surgery, Gynecology and Obstetrics*, October, 1944) describes a method of resting the colon according to the principles enunciated by Devine, but with the addition of a double tube with a balloon attached. The balloon and tube are passed into the colon through the caecostomy or loop colostomy opening and inflated to form a barrier to obstruct the passage of any fæces into the diseased segment. One lumen is used to inflate the balloon and the second to wash out the bowel distal to the balloon. The details as to the type of tube and balloon are given and the tests used to arrive at a suitable weight and rigidity when inflated are described. Reproduction of skiagrams shows the balloon shutting off the barium enema. The author points out that no additional operation or anæsthetic is required, and if obstruction is present or imminent, this method, by permitting acute conditions to subside, may convert an inoperable into an operable lesion.

Transmesenteric Hernia.

G. D. CUTLER AND H. W. SCOTT (*Surgery, Gynecology and Obstetrics*, November, 1944) report two cases of herniation through mesenteric defects in addition to two previously reported by the former author. They have also assembled 46 other well-documented cases from the literature, and on this basis they review the whole subject. Intraabdominal hernia is only a rare cause of intestinal obstruction, and statistics indicate that of all such herniæ, those through mesenteric defects account for only about 11%, so that transmesenteric hernia is among the least common causes of intestinal obstruction. Holes in the mesentery were described by early anatomists, and according to one authority are found about once in every 400 cadavers. The majority of these openings appear to occur in the ileo-caecal region. Less commonly they are found in the mid-ileal region, and still more rarely in the jejunum. An occasional case shows multiple fenestrations throughout the length of the mesentery, and a case has been reported in the meso-sigmoid. Trauma, inflammation and congenital defects have been advanced as ætiological factors. In eight of the patients under review there had been a history of some form of abdominal trauma, but in all except one case the edges of the defect were smooth and rounded, which would hardly be expected if trauma was in fact the cause. The frequency of the ileo-caecal region as the site of the opening has led to the theory that appendiceal inflammation may lead to the condition. However, the authors consider this hypothesis lacking in proof. Most authorities subscribe to the developmental theory of origin. It is of interest to note that multiple fenestrations of the mesentery are commonly found in the goose. When a small knuckle of bowel prolapses through one of these defects, distension of the knuckle probably occurs with the formation of a "gas trap" mechanism, leading to further lengths of bowel being drawn through. In one of the reviewed cases, the whole of the small bowel had prolapsed through a mesenteric opening only three inches in diameter. The familiar changes associated with intestinal strangulation occur, and may be rather rapid. The clinical picture is one of acute intestinal strangulation without any characteristic features. The specific cause of the obstruction was not recognized in any of the present series of cases until laparotomy was performed. Treatment follows the usual lines of reduction or resection according to the state of the bowel. The authors feel that when resection is necessary, a Mikulicz resection offers the patient the best chance of survival.

Thiouracil in Pre-Operative Preparation of Thyreotoxic Patients.

SINCE Astwood in 1943 reported his first experiments in the use of thiourea and thiouracil in human beings suffering from thyreotoxicosis, the question has arisen as to how far the use of this class of drugs will replace operative treatment. The question is still undecided, but H. M. Clute and R. H. Williams (*Annals of Surgery*, October, 1944) report their opinions after treating 115 thyreotoxic patients either with thiouracil alone or with thiouracil and thyreoidectomy. In the present state of knowledge they consider that thyreoidectomy is still indicated in the treatment of patients with very large goitres, of patients who live far away and cannot attend regularly for check-up examinations, of patients who through ignorance or temperamental difficulties cannot be depended on to follow medical instructions faithfully, and of patients who show undesirable reactions to thiouracil. They consider surgery necessary in toxic adenomatous goitre on account of the large mass of tissue in the neck and the danger of later substernal development. Single discrete adenomata are treated surgically, as the authors consider these lesions as premalignant. Fifteen patients with recurrent or persistent toxicity after thyreoidectomy have been treated successfully with thiouracil alone and further surgery has not been necessary in these cases. Patients who are to receive thiouracil as pre-operative treatment are admitted to hospital for basal metabolic tests and blood examinations. Thiouracil is started, and in a few days the patients are allowed to go home to continue this except where they are exceptionally toxic or cardiac involvement is present. They are allowed to carry on with their normal work, but attend at fortnightly intervals for check examinations. Pre-operative preparation usually takes about five weeks, but patients who have previously had iodine therapy take longer to settle. About 10% of patients show untoward symptoms and signs from thiouracil administration. The most serious condition reported is agranulocytosis. In some cases a leucopenia occurs, but it may be possible to continue administration of the drug to these patients, though in reduced dosage. Several patients in the authors' series developed a morbilliform rash with itching, but this subsided in spite of continuance of the treatment. A few patients developed urticaria, and in its more severe forms this may necessitate withdrawal of the drug. In most cases the gland became smaller and firmer during the preparation. At operation the glands were not so vascular as when no treatment had been given. The gland was at times densely adherent to surrounding tissue and tissue planes were difficult to define. More bleeding was encountered in some of the cases in which thiouracil had been given than in those in which iodine had been used, and more time had to be spent in its control. The post-operative course after the use of thiouracil was remarkable only for its smoothness when adequate time had been spent in this preparation. Thiouracil was stopped four to six days after operation. Cyclopropane and oxygen was the anæsthetic of choice and no special problems were presented to the anæsthetist. One post-operative fatality is reported in this series, that of a patient who had had auricular fibrillation for a year prior to the operation, the fibrillation having ceased a few days before the thyreoidectomy. She died three hours after an uneventful operation, probably from an embolus. The late results have been very satisfactory, only one patient having a slight recurrence of toxicity, which was easily controlled by small doses of thiouracil for a few weeks. The authors think it probable that post-operative myxœdema may be seen in an occasional patient who has considerable thyreoiditis associated with hyperplasia in the gland.

Perforating Abdominal Injuries.

H. E. SLOAN (*Surgery, Gynecology and Obstetrics*, October, 1944) reports an investigation at the Johns Hopkins Hospital of perforating abdominal injuries in the period 1925 to 1943. He compares the earlier and later halves of this period. There has been a marked reduction in mortality which the author attributes mainly to frequent blood transfusions and the use of sulphonamides; but he draws attention to the use of the Miller-Abbott tube and improved anæsthetic methods. He points out that conditions such as those prevailing at Dunkirk and during the bombing of Britain make it more difficult for the surgeon to save life, but even under those conditions the mortality reported is astonishingly low.

British Medical Association News.

SCIENTIFIC.

A meeting arranged by the Section of Neurology, Psychiatry and Neurosurgery of the New South Wales Branch of the British Medical Association, in conjunction with the Mental Hospitals Department, was held at the Mental Hospital, Callan Park, on October 26, 1944. The meeting took the form of a series of clinical demonstrations.

Presenile Dementia.

Dr. A. T. Edwards showed a male patient, aged seventy years. His family history was clear, with the exception of a younger brother who was in the hospital in 1918 suffering from *dementia paralytica*. The parents were stated to have died of "senile decay" and to have shown no mental deterioration. Similarly two brothers and three sisters lived to be over seventy and were "quite clear mentally". The patient was stated to have been free from any serious illness during his life. Since leaving school he was engaged in business in the city, being sales manager when he retired at the age of fifty-five years. Retirement was due to failing memory, so that the actual age of onset of the condition was probably in the vicinity of fifty-three years. His memory gradually became worse, and he developed delusions of robbery, which finally led to his certification six years prior to the meeting.

On his admission to hospital, he was in good physical health. His blood pressure was 144 millimetres of mercury (systolic) and 92 (diastolic). His speech was noted as "slightly thickened", but there were no focal signs. He was depressed and dull, with auditory hallucinations. He continually complained that his head was out of shape and that he could not think properly. He was disorientated for place and time, and his memory was grossly impaired for both recent and remote events. In 1938 encephalography revealed extensive cortical atrophy of each hemisphere.

Dr. Edwards said that whilst the patient was in hospital, he had been dull and retarded and had continually complained of his head "not working right", apparently expressing some awareness of his condition. Memory had deteriorated still further, and he failed to recognize the medical officers whom he has seen almost daily for seven years. He was resentful and resistive to examination. He displayed exaggeration of all tendon reflexes with the exception of the jaw jerk. The plantar reflex on the right side was doubtfully extensor; it was difficult to elicit owing to his resistiveness. He displayed some dysarthria. No agnosia and no apraxia was present. Writing to dictation was impaired, and he was incapable of spontaneous writing. The widespread cortical atrophy, the emphasis on the memory defect and the deterioration of intelligible, meaningful speech indicated that the condition was probably Alzheimer's disease, despite the absence of the hyperkinetic symptoms that were generally described in that condition.

Dr. Edwards next showed a female patient, aged sixty-one years. Nothing relevant was learnt from the family history. She was an average scholar. After leaving school she worked as a domestic servant until her marriage at the age of nineteen years. Twenty years later she divorced her husband and remarried soon afterwards. Neither marriage was happy. Her physical health had been good, except for cholecystitis and osteoarthritis of the knee in 1938. The basal metabolic rate in 1943 was +13%. The mental condition had developed during the seven years previously to her admission to hospital, placing the age of onset at approximately fifty-four years. Her husband complained that during this time her memory "was terrible—she was always forgetting what she had done and what she was going to do". Certification was due to a suicidal attempt, motivated by sexual delusions concerning her husband.

On her admission to hospital her physical condition was good. Her blood pressure was 160 millimetres of mercury (systolic) and 85 (diastolic); a mitral systolic murmur was present. Her memory was grossly impaired. The day after admission to hospital she stated that she had been in hospital for five years. She was disorientated for all spheres and could not even name her children. She could give no adequate account of her life. She was extremely restless both by day and by night.

Dr. Edwards said that since her admission to hospital she had rapidly deteriorated, both mentally and physically. She was restless, continually rubbing her arms and hands and picking at the bed clothes if in bed. She displayed echolalia and perseveration with stereotypy of movement. Her speech was invariably incoherent, generally a low mutter and quite unintelligible. She was resistive to examination. No focal signs had been elicited. The tendon reflexes were all diminished. It was considered that the condition belonged to the hyperkinetic type of Alzheimer's disease.

Hysterical Amnesia.

Dr. Edwards's third patient was a male, aged eighteen years, who had been admitted to hospital on October 7, 1944; he had been sent from a service hospital under National Security Regulation Number 47, with the diagnosis of manic-depressive psychosis. His parents were alive and healthy. He had two brothers, one of whom suffered from asthma. His maternal grandmother was in the hospital suffering from confusional psychosis. The patient was the eldest in the family. He had walked and talked at the usual ages, but was considered a "nervy" baby. He attended school until the age of fifteen years, but failed at the Intermediate Certificate examination. Although his school work was good, he was always nervous at examinations. After leaving school he worked mainly as a store boy in the railway department until he enlisted in the Royal Australian Air Force six months prior to his admission to hospital. Since his enlistment he had expressed intense dread of being sent out of Australia and especially of having to fight the Japanese. He was stated to have been always bright and cheerful, but reserved. He was fond of sport, but took no interest in the opposite sex. His mother denied showing any preference for him or of spoiling him; but the grandmother stated that the mother had always "molly-coddled the boy", and that she was even terrified to allow him to be taught to swim in case something dreadful happened. Some little time before the onset of the illness he was said to have fired a bullet through a tent and to have been severely reprimanded. Prior to his admission to the hospital he was said to have tried to strangle himself with his identity disk cord and later with his pyjama trousers.

On his admission to the hospital, he was quiet and well behaved, and when questioned the following day, displayed complete amnesia for all events up to the time of his arrival there. This complete amnesia remained unchanged until October 24. He had continually failed to recognize his parents, saying that he knew they were his parents only because he had been told so. There has been no amnesia concerning any events since his admission to hospital. Recently he saw a picture in a daily newspaper, and after twenty-four hours' perturbed thought he recognized it as being taken at the Clyde railway yards where he had previously worked. At the time of the meeting he remembered his working days and his school days, but was unable to remember his home life or any of his people. He had complete amnesia for all his recreations and for his life in the Royal Australian Air Force. He said he had been told that he hated women, and he thought that this was true, as he felt uncomfortable in the presence of the female medical officer. He said that he had no interest in sex and no sex feelings, and that when the other patients talked of sex matters it seemed to him just a big joke.

Dementia Paralytica in a Young Man.

Dr. S. G. Sandes showed a man, aged twenty-six years, who had been admitted to hospital on September 8, 1944. He was a "fairly good" scholar and a first-grade cricketer. He worked as a textile cutter until he was called up for military service in June, 1941. He admitted promiscuous sexual intercourse and stated that when he was aged twenty-one years he developed a penile sore, which was treated by a doctor with ointment only. He served in the Northern Territory and in New Guinea and was returned medically unfit in January, 1944. He was admitted to an Australian general hospital with the diagnosis of congenital taboparesis. He was sent to another Australian general hospital, where he had two courses of treatment with "Mapharsen" and one with "Bismol". He was then admitted to yet another Australian general hospital to be investigated for a possible cerebral tumour or cerebro-spinal syphilis. X-ray examination of the skull and examination of the fundi, visual acuity and the blood picture gave negative results. The cerebro-spinal fluid contained one cell per cubic millimetre, 100 milligrammes *per centum* of protein and 680 milligrammes *per centum* of chlorides; the fluid reacted to the Wassermann test. He was readmitted to the first Australian general hospital to which he had gone, and showed "marked mental deterioration" as compared with his condition six months earlier. The cerebro-spinal fluid contained one cell per cubic millimetre, and the gold sol test produced the result "4431110000".

On his admission to the Mental Hospital, Callan Park, the patient was seen to be a strongly built young man. No abnormality was detected in the heart, lungs or abdomen; his systolic blood pressure was 120 millimetres of mercury and his diastolic pressure was 70. He showed considerable circumoral tremor, tremor of the tongue and coarse tremor of the hands and fingers. Articulation was slurred. His pupils were medium and equal in size; they reacted to accommodation and somewhat sluggishly to light. His knee jerks were brisk and the plantar reflexes were extensor in type. No gross sensory changes were noted. His gait was unsteady and broad-based, but Romberg's sign was not elicited. His face showed Parkinsonian loss of expression. He was dull, slow, childish, and simple and restricted in ideation. Memory was somewhat impaired. In view of his position, he showed a mild foolish euphoria. He was untidy, careless of appearance and mentally deteriorated. The blood reacted to the Wassermann test. The cerebro-spinal fluid also reacted to the Wassermann test; it contained eighteen cells per cubic millimetre; the globulin and Takata Ara tests produced positive reactions, and the gold sol test produced the figures "5554431100".

Carbon Monoxide Poisoning.

Dr. Sandes also showed a patient suffering from carbon monoxide poisoning. He was a chief petty officer in the Royal Australian Navy, aged forty-eight years, and had been admitted to hospital on October 5, 1944. The patient's wife had committed suicide on August 31, 1944. On September 25, the patient was found by a neighbour, unconscious in his garage, with a tube beside him leading from the exhaust pipe of his motor-car engine. He was removed by ambulance to a district hospital, placed in an "iron lung" and treated for carbon monoxide poisoning. Next day he was transferred to the Reception House, where he was found to be "resistive, morose, wakeful and unable to give any account", and was placed in restraint. On the following day he denied any attempt at suicide and was resentful to questioning, resistive and confused. Five days later he was "well behaved and quiet".

On his admission to the Mental Hospital, Callan Park, he showed little physical abnormality. The pupils were small and reacted to light and accommodation. No deep tenderness of muscles or nerve trunks, no ataxia and no pareses, tremors or undue muscular rigidity were found, although his face lacked expression. The knee jerks and other deep tendon reflexes were exaggerated. The systolic blood pressure was 125 millimetres of mercury and the diastolic pressure 70. The pulse rate was 68 per minute. He had sores on the right thumb and index finger, which appeared to be recent burns.

The outstanding feature of his mental condition was a disturbance of memory. Memory for remote events was good—he named his schoolmaster, described boyhood surroundings *et cetera*. For less remote events his memory was grossly impaired. He was unable to give any reliable account of his life in the Royal Australian Navy beyond the fact that he joined H.M.A.S. *Australia* at Chatham in about 1919. The amnesic period was not well defined, and he was unable to give any clear-cut "last memory". So far as he knew, Britain was at peace. He was disorientated for time. For recent events, amnesia was complete. He politely but firmly rejected the idea of his wife's suicide, and his own attempt. There was complete failure of retention, and information imparted to him, whether emotionally toned or impersonal, was forgotten within minutes or hours. The memory defect was of Korsakov type, except that he fabricated comparatively little and generally admitted his memory loss. He lacked interest and initiative, and gave the impression of being detached and remote. He expressed no emotion other than mild surprise when discussing his illness and present situation. One week after his admission to hospital he showed a slight improvement in memory of his work in the Royal Australian Navy since 1919, but no other change.

Dementia Paralytica in Mother and Daughter.

Dr. Sandes then showed a mother and daughter suffering from *dementia paralytica*. The mother was a widow, aged forty-nine years, who had been admitted to hospital on October 30, 1941. She was the mother of sixteen children, "six or seven" of whom were stillborn. She was said to be "failing" for about two years prior to her admission to hospital. Over a period of some months before admission to hospital her behaviour indicated increasing mental and moral deterioration; she became slovenly and finally reached the stage of being unable to care for herself.

On her admission to hospital she was demented and indifferent, except for a few semi-coherent mutterings about "poison" or "going home". Her pupils did not react to light. The knee jerks were active. The blood yielded slightly positive reactions to the Wassermann, Kline and Boas tests. The cerebro-spinal fluid reacted to the Wassermann test; it contained two cells per cubic millimetre, and it yielded a slightly positive reaction to the globulin test and a "21110000000" reaction to the gold sol test. Dr. Sandes said that a course of nine malarial rigors produced no improvement. The patient no longer uttered any intelligible words, but simply babbled. She was gluttonous and obese. She did not recognize her daughter in the same ward, but ineffectually "mothered" another patient.

The daughter had been admitted to hospital on September 15, 1941, at the age of sixteen years. Her sister stated that the patient could "hobble along" until three months before her admission to hospital, when she had a "seizure". The patient's sister next in age had been treated for syphilis.

On her admission to hospital the patient could remember the name of only one of her sisters. She had never been to school. Her mental status was that of a low-grade imbecile. Bossing of the frontal bases, Hutchinson's teeth and interstitial keratitis were present; the right leg was paralysed, adducted and flexed, the left arm was paralysed and contracted in flexion. The pupils did not react to light. The knee jerks were exaggerated. The cerebro-spinal fluid contained an increased amount of globulin and the protein content was forty milligrammes *per centum*. The gold sol test produced a "45554422110" reaction. The blood reacted to the Wassermann and Kline tests. Dr. Sandes said that a course of seven malarial rigors in December, 1941, had produced no improvement in her mental condition. She had, however, put on considerable weight since her admission to hospital.

(To be continued.)

NOTICE.

THE General Secretary of the Federal Council of the British Medical Association in Australia has announced that the following medical practitioner has been released from full-time duty with His Majesty's Forces and resumed civil practice as from the date mentioned:

Dr. N. A. Walker, 5, Hill Street, Roseville, New South Wales (March 9, 1945).

Post-Graduate Work.

A GENERAL REVISION COURSE AT SYDNEY.

THE New South Wales Post-Graduate Committee in Medicine announces that a general revision course will be held in Sydney from Monday, May 21, to Saturday, June 2, 1945, inclusive. The programme for the course is set out below.

Applications to attend the course should be made as soon as possible to the Secretary, New South Wales Post-Graduate Committee in Medicine, 131, Macquarie Street, Sydney. Telephone: B 4606. Applications should state home address and Sydney address, and should be accompanied by a cheque for the amount of the fee, made payable to the committee.

The fee for the course is £5 5s. For medical officers of the defence forces, demobilized officers, members of the public service and hospital residents, the fee will be £2 12s 6d.

A special charge will be made for the luncheon, and arrangements will be made at registration or during the course for those who wish to attend.

The supervisor of the course is Dr. William Wood.

Monday, May 21.

The Stawell Hall, 145, Macquarie Street, Sydney.

Morning.—9 to 10: Registration. 10 to 10.30: Address by Dr. S. A. Smith, Chairman of the Post-Graduate Committee. Address by Surgeon Rear Admiral J. A. Maxwell, C.V.O., C.B.E., F.R.C.S. (Ed.), R.N. 11 to 11.30: "Some Practical Views in Medico-Legal Work", Dr. Stratford Sheldon. 11.45 to 12.15: "Troublesome Diseases in Early Childhood", Dr. Edgar Stephen.

King George V Memorial Hospital, Camperdown.

Afternoon.—2 to 3: "Prolapsus Uteri", Dr. H. H. Schlink, Dr. C. Chapman. 3 to 3.45: "Laboratory Investigation in Gynæcology", Dr. Mary Heseltine. 4 to 5: "Common Gynæcological Symptoms and their Interpretation", Dr. F. A. Maguire.

Tuesday, May 22.

Royal Prince Alfred Hospital, Camperdown (Lecture Theatre).

Morning.—9.15 to 9.45: "Common Skin Diseases in General Practice", Dr. J. Belisario. 10 to 10.30: "Migraine", Dr. W. Lister Reid. 11.15 to 11.45: "Dangers in Drugs", Dr. Alan S. Walker. 12 to 12.30: "Common Nervous Diseases", Dr. C. G. McDonald.

Afternoon.—2 to 2.30: "The Use of Thio Drugs in Thyreotoxicosis", Dr. H. R. G. Poate. 2.45 to 3.15: "Disabilities of the Knee Joint", Dr. L. G. Teece. 4 to 4.30: "Physiotherapy in General Practice", Dr. B. G. Wade.

Wednesday, May 23.

Royal North Shore Hospital, St. Leonards (Nurses' Lecture Theatre).

Morning.—9.15 to 9.45: "The Technique of and the Indications for and against Spinal Puncture", by Dr. R. A. Money. 10 to 10.30: "The Modern Treatment of Urinary Tract Infections", Dr. Colin Edwards. 11.15 to 11.45: "The Role of the General Practitioner in Plastic Surgery", Dr. Basil Riley. 12 to 12.30: "Diabetes Mellitus", Dr. W. Wilson Ingram.

Afternoon.—2 to 3: Demonstration, "Allergy", Dr. Bernard Riley. 3 to 4.30: Demonstration of chest cases, Dr. Bruce White and Dr. M. P. Susman.

Thursday, May 24.

The Royal Hospital for Women, Glenmore Road and Oxford Street, Paddington (Lecture Room, Second Floor).

Morning.—9 to 9.45: "Demonstration of Perineal Repairs", Dr. H. A. Ridler. 10 to 10.45: "Termination of Pregnancy", Dr. Gordon Lowe. 11.30 to 12.15: "Sterility", Dr. Bruce Hittman.

Afternoon.—2 to 2.45: "Lower Segment Cæsarean Section", Professor Bruce Mayes. 3 to 3.45: "The Rh Factor", Dr. Kathleen Winning.

Royal Prince Alfred Hospital.

Evening.—Clinical evening.

Friday, May 25.

The Prince Henry Hospital.

Morning.—9.30 to 10.30: Ward demonstration of medical cases, Dr. S. A. Smith. 11.15 to 12.30: Ward demonstration of medical cases, Dr. S. A. Smith.

Afternoon.—2 to 2.45: "Some Remarks on Intestinal Obstruction", Dr. T. M. Furber. 3 to 4.30: Demonstration of infectious diseases (in nurses' lecture theatre and wards), Dr. N. J. Symington.

Saturday, May 26.

Broughton Hall Psychiatric Clinic, Wharf Road, Leichhardt (leave Leichhardt Tram at Glover Street).

Morning.—9.30 to 11: Demonstration of early nervous and mental disorders, Dr. S. Evan Jones and staff.

Monday, May 28.

Sydney Hospital, Macquarie Street, Sydney (Maitland Lecture Theatre).

Morning.—9.15 to 9.45: "General Appearances in Disease" (with lantern slide demonstration), Dr. E. H. Stokes. 10 to 10.30: "The Treatment of External Inflammatory Conditions of the Eye", Dr. C. K. Cohen. 11.15 to 11.45: "Urology in General Practice", Dr. Keith Kirkland. 12 to 12.30: "Tumours of the Breast", Dr. R. Rawle.

Afternoon.—2 to 3: "Gynæcological Problems", Dr. R. I. Furber and Dr. H. K. Porter. 3 to 3.30: "Common Diseases of the Ear, Nose and Throat and their Treatment", Dr. B. Blomfield. 4.15 to 5: "Ward Rounds in Common Medical Diseases", Dr. G. C. Willcocks.

Tuesday, May 29.

Saint Vincent's Hospital, Darlinghurst (Students' Lecture Theatre).

Morning.—9.15 to 9.45: "Useful Practical Points in Anæsthesia", Dr. Stuart Marshall. 10 to 10.30: Dr. Edward G. MacMahon. 11.15 to 11.45: "Some Important Indications for Radiotherapy", Dr. C. F. de Monchaux. 12 to 12.30: "Gastric Carcinoma", Dr. J. E. Sherwood.

Afternoon.—2 to 2.30: "The Management of Varicose Veins and Common Rectal Conditions", Dr. V. M. Coppleson. 2.45 to 3.15: "Sciatica and Allied Problems", Dr. I. Douglas Miller. 4 to 4.30: "Practical Problems in Cholecystitis and Cholecystectomy", Dr. W. Maxwell.

Wednesday, May 30.

The Women's Hospital, Crown Street, Surry Hills (Lecture Theatre).

Morning.—9.15 to 9.45: "The Place of X Rays in Obstetrics", Dr. T. Dixon Hughes. 10 to 10.30: "The Role of Blood Transfusion in Obstetrics", Dr. Ruth Heighway. 10.45 to 11.15: "Dystocia", Dr. A. J. Gibson. 11.45 to 12.15: "Modern Conceptions of Toxæmia", Dr. E. Holman (Fellow in Obstetrics). 12.15 to 12.45: "The Care of the Cardiac Patient", Dr. R. Jeremy and Dr. H. McCredie.

Afternoon.—2 to 2.45: "Sepsis", Dr. John Chesterman. 3 to 3.30: "Indications for Forceps", Dr. R. B. C Stevenson. 3.30 to 4: Film on "Caudal Analgesia".

Thursday, May 31.

Lewisham Hospital, Lewisham (Out-Patient Department).

Morning.—9.15 to 9.45: "Sinusitis and its Treatment", Dr. H. H. Harrison. 10 to 10.30: "The Anæmias", Dr. Leo Flynn. 11.15 to 11.45: "Manipulation: Indications and Uses", Dr. N. Little. 12 to 12.30: "Fractures of the Wrist", Dr. John Hoets.

Afternoon.—2 to 4: Demonstration of clinical cases, members of the honorary medical staff.

The R. H. Todd Assembly Hall, 135, Macquarie Street, Sydney.

Evening.—British Medical Association Branch Meeting: "Blast Injuries."

Friday, June 1.

The Royal Alexandra Hospital for Children, Camperdown (Students' Lecture Theatre).

Morning.—9 to 10: Removal of Tonsils and Adenoids. 10 to 10.45: "Anæmias in Children", Dr. Lorimer Dods. 11.15 to 12: Demonstration of medical cases (including infantile paralysis), Dr. R. J. Taylor. 12 to 12.45: Demonstration of medical cases, Dr. R. A. Green.

Afternoon.—2 to 2.45: Demonstration of surgical cases, Dr. C. H. Wesley. 2.45 to 3.30: Demonstration of surgical cases, Dr. Gordon Tait. 4 to 4.45: Demonstration of pathology cases, Dr. D. Reye.

Saturday, June 2.

Sydney Hospital, Macquarie Street, Sydney (Library of the Kanematsu Institute).

Morning.—9.30 to 11.30: Demonstration of blood and serum transfusion, Major R. J. Walsh.

Correspondence.

PENICILLIN IN TETANUS.

SIR: From the last sentence of your current comment on "Penicillin in Tetanus" in your issue of March 24, 1945, I thought that the following notes on two cases of tetanus treated with penicillin might be of interest.

B.S.B., a male, aged twenty years, a fireman, was seen on January 8, 1945. He had left inguinal adenitis due to two septic wounds on his left leg and ankle, of two weeks' duration, treated at home and then apparently causing little trouble. Later in the day he developed pain in his back, severe in intensity, and some trismus was present. He was admitted to hospital and was at once given 40,000 units of tetanus antitoxin and 15,000 units of penicillin intramuscularly three-hourly, till he had had 200,000 units. Temperature on admission was 100·4° F., pulse 100. Temperature rose to 101·4° F. on January 9, 1945, and was subnormal from January 13, 1945. He was discharged cured on January 15, 1945, and resumed his duties soon after.

K.D.B., aged fifteen years, a school boy, was first seen on January 27, 1945. There was a healed wound on his left middle toe, sustained three weeks previously, which had been treated at home. Temperature was 102·4° F., pulse 100, with trismus, and some pain in his back was present. He was admitted to hospital and given 20,000 units of tetanus antitoxin and 15,000 units of penicillin intramuscularly three-hourly, to a total of 200,000 units. His temperature was again 102·4° F. on January 28, 1945, but was normal on January 30, 1945, and remained so till his discharge on February 3, 1945.

I think both these patients would probably have recovered with antitoxin only. Neither developed any tetanic convulsions. They were typical mild cases of tetanus, the noteworthy point about each of them being the smooth progress of recovery, with trismus lessening each day and the pain in the back subsiding quickly. I attribute this to penicillin, which so altered the usual course of the disease as to lead to the opinion that penicillin is of the greatest value in tetanus.

Yours, etc.,

PAUL E. VOSS.

Rockhampton,
Queensland,
March 26, 1945.

SIR: In the issue of THE MEDICAL JOURNAL OF AUSTRALIA of March 24, 1945, two cases of tetanus in America successfully treated with penicillin were described. I should like to report a similar case successfully treated with penicillin in Prince Henry's Hospital, Melbourne.

The patient, a well-nourished Scot, aged forty-seven years, was admitted on January 21, 1945, with well-developed tetanus, giving a history of scratching his forehead nine days previously; seven days after he developed quite suddenly lockjaw.

On admission, that is, two days later, he showed a very small infected puncture wound on the forehead and marked *risus sardonicus*. The following day rigidity had become generalized, whilst two days later spasms commenced.

He was treated as follows:

1. Anti-tetanic serum: 100,000 units *statim* and 20,000 units daily intravenously for five days.
2. Penicillin: 20,000 units three-hourly for eight days—a total of 1,280,000 units being given.
3. For sedation: "Avertin"—one gramme per kilogram of body weight was used twice daily for eight days.

The patient was discharged on February 19, 1945—twenty-nine days after admission—entirely cured.

Although no definite proof is available, I am of the opinion, based on the severity of the symptoms exhibited, that this patient would not have recovered without the use of penicillin in conjunction with the antitetanic serum.

It is of interest that bilateral varicose ulcers of some years standing, from which this patient was also suffering, healed dramatically under systemic penicillin.

Yours, etc.,

HOWARD A. TOYNE, M.B., B.S.
Resident Medical Officer.

Prince Henry's Hospital,
Melbourne,
March 31, 1945.

MEDICAL RELIEF UNITS.

SIR: I think there is an urgent relief job to be done at once, where charity is supposed to begin. I refer to the plight of our Eighth Division. We hear little about the boys except when a war loan appeal is in progress, but doubtless the recently published statement gives only a pale account of their sufferings.

Could we organize a small medical unit to go into voluntary imprisonment and take stores to those in the bad outlying camps? At the worst, if the Japanese would not play and grabbed the stores, we could still work among the boys. The psychological effect of practical evidence that they have not been altogether abandoned would surely compensate for the difficulty of working without stores. (I heard the other day that Bert Coates is operating with domestic tools.)

If the Japanese would agree—through Geneva or the Vatican or Russia or someone—to grant safe passage to a relief ship, we could take in enough medical stores to last the unit for the duration. Such a unit could consist, say, of six medicos, six sisters and a dozen orderlies.

I appeal to all our "Old Diggers" in the profession as well as those now languishing in the army with nothing to do, not to dismiss this idea as fantastic and impracticable. After all, we should be able to count on personnel, as we all accepted the risk of imprisonment when we volunteered for active service. The great difficulty as I see it is red tape, which can always be overcome if enough real fighters are interested.

Yours, etc.,

MARY THORNTON.

Warrandyte,
Victoria,
March 27, 1945.

MASS RADIOGRAPHY OF THE THORAX FOR CIVILIANS.

SIR: I was interested to read in THE MEDICAL JOURNAL OF AUSTRALIA of the twenty-fourth instant a letter, over the signature of T. W. Lipscomb, *re* the installation of an X-ray plant in Maitland, New South Wales.

One statement therein requires correction, and I am sure that you will be pleased to acquaint the profession in general that an X-ray centre was opened for free mass radiography in this municipality on April 15, 1943.

Probably this was the first provincial town to instal an X-ray apparatus for this purpose, and the installation was brought about as the result of recommendations made by the medical officer of health, Dr. G. F. Beck, and the health inspector, Mr. D. J. Stanley.

The council, industries, the unions and private citizens contributed the sum of £1,000, to which the Government added a similar amount.

The centre is open to the residents of this and neighbouring municipalities and approximately 4,500 have been X-rayed to date.

I desire to congratulate Maitland on its entry into this field of community service.

Yours, etc.,

I. S. LANCASTER,
Town Clerk, Town of Newtown and Chilwell.

Newtown,
Geelong,
Victoria.
March 27, 1945.

THE PHARMACEUTICAL BENEFITS ACT, 1944.

SIR: I would like to assure Dr. Collins that he is pardoned for suspecting that I am more interested in the scheme on political rather than on humanitarian grounds in spite of his being quite wrong. I have not the slightest political interest in the matter. I feel that the public is in great need of help in all things relating to its health. To find the truth and decide how best the profession can help without serious harm to itself are my interests in the subject.

There are conflicting facts in the letters in answer to mine. To give one example:

"The Council's objection is based mainly on grounds that money to be expended . . . could be much better spent in other directions."

"We are only concerned with the main issue, whether the bureaucrat is to control the profession." (The same writer later urges Council to take an uncompromising stand and demand a pledge!)

Dr. Collins does not use the word "main", but his meaning is clear. His objection is that the Government won't pay for all prescriptions.

It is all somewhat confusing—socialism, politics, personalities, tigers and bureaucrats are mixed up with it all—and, I'm sorry, I nearly forgot, the patient. He is in it, too.

It has been an interesting discussion. I always thought communists fomented strikes. I have expressed the hope that similar tactics might be averted, but I have been called a communist. Yes, it has been interesting.

Yours, etc.,

C. H. W. LAWES.

Australian Army Medical Corps,
Australian Imperial Force,
April 5, 1945.

THE TREATMENT OF HÆMORRHOIDS BY INJECTION.

SIR: Dr. Barnett's observations on the injection treatment of hæmorrhoids, I think, require further amplification.

The 20% solution of carbolic acid in equal parts of glycerin and water is a very effective agent if used for a specific purpose and according to a correct technique. As Dr. Barnett states, it should be injected into the centre of the pile itself. Its chief action is the prompt cessation of bleeding accompanied by the rapid shrinkage of the pile mass, and my practice is to confine its use to piles actually "weeping" blood or whose mucosa is of a raw plush-like texture signifying ready bleeding. The injection is made through the mucosa of the pile, that is, above the mucocutaneous junction. The dose into each pile is in the order of two to five minims, depending on its size, and in any case

should not be sufficient to cause tension (evidenced by immediate pain) within the pile. The use of a tuberculin syringe both facilitates the dose measurement and minimizes obstruction to visibility through the speculum. In no case should the injection be made into an acutely inflamed or thrombosed pile, even though it may be bleeding, nor should it be made through skin or transitional epithelium external to the muco-cutaneous junction. Most such piles are best injected through a speculum (adequately withdrawn to bring them into view), but occasionally everted piles may be injected *in situ* as long as they are promptly replaced into the anal canal beyond the grip of the external sphincter. One such injection into each pile usually suffices to sclerose it and stop bleeding, and only occasionally is a second series necessary. Such treatment only stops bleeding and greatly shrinks the pile masses. The cure of eversion or prolapse of the pile-bearing area still requires intraanal submucosal injections with 5% carbolic acid in almond oil into and above the upper boundaries of the pile-bearing area.

Providing the operator is competent to interpret the tissues presenting into the speculum and strictly observes the foregoing rules, he should avoid the painful complications which might tend to bring the technique into disrepute. Perianal and ano-rectal tissues are resistant to infection, tolerant to abuse, but once grossly damaged notoriously slow and difficult to heal. A final tip to those who would treat piles, is to remember that uncomplicated piles are painless, and if severe pain is the presenting symptom, first, by assiduous search, exclude the presence of an anal fissure before inserting a speculum. My experience gives me the impression that anal fissure ranks very high in the doubtful honour of going undiagnosed.

Yours, etc.,

R. D. Davey.

Croydon Park,
New South Wales,
April 4, 1945.

Naval, Military and Air Force.

APPOINTMENTS.

The undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 66, of April 5, 1945.

Naval Forces of the Commonwealth.

Permanent Naval Forces of the Commonwealth (Sea-Going Forces).

Emergency List.

Transfer to Retired List et cetera.—Surgeon Commander William Edgar Roberts is transferred to the Retired List and reappointed for temporary service, dated 18th February, 1945.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Fixing Rates of Pay.—Surgeon Lieutenant James Stuart Guest to be paid the rates of pay and allowances prescribed in the Naval Financial Regulations for Surgeon Lieutenant-Commander (on promotion) whilst acting in that rank, dated 20th January, 1945.

DECORATIONS.

Surgeon Commander James Martin Flattery, H.M.A.S. *Australia*, has been mentioned in dispatches.

Obituary.

MINNIE FRANCES VARLEY.

We regret to announce the death of Dr. Minnie Frances Varley, which occurred on March 30, 1945, at Melbourne.

JAMES WILLIAM BARRETT.

We regret to announce the death of Sir James William Barrett, which occurred on April 6, 1945, at Melbourne.

Nominations and Elections.

The undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Graham, John Wedgwood, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

Henry, Margaret Tress, M.B., B.S., 1944 (Univ. Sydney), Saint George District Hospital, Kogarah.

Baird, John Speir, B.D.S., 1927 (Univ. Sydney), D.D.Sc., 1932 (Univ. Sydney), M.B., B.S., 1944 (Univ. Sydney), 175, Macquarie Street, Sydney.

Gayst, Henry, M.B., B.S., 1944 (Univ. Sydney), 12, Elva Avenue, Killara.

Diary for the Month.

Apr. 16.—Victorian Branch, B.M.A.: Hospital Subcommittee.
Apr. 16.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
Apr. 17.—Victorian Branch, B.M.A.: Organization Subcommittee.
Apr. 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

Medical practitioners are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All Public Health Department appointments.

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